12th Annual Report of
the National Institutes of Health

Program in Biomedical and Behavioral Nutrition Research and Training

Fiscal Year 1988

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

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NIH Nutrition Coordinating Committee
Division of Nutrition Research Coordination

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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EXECUTIVE SUMMARY

Important discoveries over the last decade in molecular biology, genetics, and immunology have opened vast new vistas in the biomedical sciences--vistas which will greatly influence nutrition in the next century. As a result, biomedical research at the National Institutes of Health (NIH), including that devoted to nutrition, is moving forward at an unprecedented pace. In fact, the coming together of many separate developments in the biomedical sciences has put the NIH on the threshold of a major leap forward in the improvement of human health. For example, the NIH is at the forefront of a rapidly growing new effort to explain the human genome--the complete set of hereditary factors, or genes, contained in the chromosomes of each cell of an individual. The massive human genome effort will take place over the next few years, and will have a profound effect upon medical and nutrition science. From future discoveries, investigators will be able to use their new knowledge about the activities of the human cell to design nutrition and drug therapies, and vaccines against a host of serious illnesses.

The heart of the new human genome effort derives from the rapid strides being made, thanks to high technology, in the understanding of the subunits of biologically important molecules: through the analysis of proteins (the tens of thousands of different molecules comprised of amino acids that perform the body's major functions); nucleic acids (DNA and RNA); carbohydrates (sugar and starches); lipids (fats); and their complex combinations and interactions in the cell. Consequently, nutrition is at the core of proper cell function. How it relates and some of the strides already developed are discussed in section 3 of this report. However, extensive speculation about where exciting developments at the cellular level will lead is beyond the scope of this report--one which is essentially devoted to the details of nutrition-related research at NIH during FY 1988. Yet the prospect of a better understanding of the human genome offers many striking possibilities for the biomedical sciences, including nutrition, in the years ahead.

Over the past 12 years, this report, published annually since 1977, has emphasized four major topics: the coordination of nutrition research at NIH, the highlights of the nutrition research program and associated program development, the fiscal year obligations in nutrition research and training, and the activities of the Nutrition Coordinating Committee (NCC) and its subcommittees. These areas are outlined in this year's four major sections which, in total, detail highlights of the nutrition research at NIH and the activities of the NCC.

The NCC was established in 1975 in the NIH Office of the Director, in recognition of the importance of nutrition as an NIH cross-cutting issue. In FY 1988, the NCC consists of representatives from 12 NIH institutes, 2 divisions, and 2 centers, with liaison representatives from other NIH offices, as well as from other Federal agencies. In 1988, the NCC became a part of the Division of Nutrition Research Coordination (DNRC). The DNRC was created to firmly establish the trans-NIH coordination of nutrition research and training as a permanent and identifiable position within the NIH and to recognize the additional responsibilities acquired over time by the NCC office. The NIH nutrition program continues to be coordinated through the NCC, which operates as an NIH-wide forum and locus for coordination of research efforts, helping the NIH avoid duplication of effort and to speak with one voice in nutrition matters.

Each bureau, institute, and division of the NIH plays a unique role in support of nutrition research, as they fund those areas related to their own particular research mission. The combination of these research areas encompasses the entire spectrum of modern biomedical nutrition research, from basic to applied, providing a diversity which is one of the NIH's greatest assets. Yet no NIH component functions in a vacuum. The NIH collaborates with other U.S. government organizations, both within and outside of the Department of Health and Human Services (DHHS); with academic institutions; with private sector firms; and with investigators in other countries who are developing and implementing research programs of mutual interest. Fostering cooperation and collaboration in nutrition research and training within the NIH is a major function of the DNRC and its NCC.

Research on the relationship of dietary factors to disease is often complicated by the complexity of the variables, the intricacy of the interactions, and the disparate nature of the analytical tools of science. After it has acknowledged the complexity of the scientific process and its often seemingly random nature, the role of this report is to give an indication of the range of nutrition-related research at NIH, some of its results, the cost overall, and how molecular biochemical, epidemiologic, and clinical dietary factors are coordinated to improve human health.

In FY 1988, as in previous years, the NIH led all Federal agencies in financial support of biomedical nutrition research and training, for an unprecedented total of $276 million. This figure represented 70 percent of all Federal expenditures and 92 percent of DHHS expenditures in biomedical nutrition research and training. The NIH nutrition research and training dollars have steadily increased during the past decade, growing from $106 million in 1978 to $276 million in FY 1988. This represents an increase of 160 percent (33 percent if dollars are adjusted for inflation). The NIH nutrition research and training dollars have consistently represented 3 to 4 percent of total NIH obligations since 1977.

This report is not designed to give a comprehensive description of all nutrition research supported by the NIH. The agency funded more than 2,000 nutrition research and training projects in 1988; including a description of each would exceed the scope of this report. However, we have tried to convey its range and diversity through selected research highlights which involve peer-reviewed studies funded by many different institutes.

The research highlights portion of this report, section 3, covers "Nutrition and AIDS," "Nutrition and Behavior," the "Nutrition and Human Genome Research," and "Nutrition and Disease Prevention." Many clinical studies have been emphasized in this section along with some animal research. Also, the science and associated technology have been discussed that are a part of the rapidly growing field of molecular research--the discipline designed to explain the activity of biologically important molecules. If scientists understand the precise structure of components on the surface of cells, they may be able to work with those elements to selectively control their activity. As detailed in section 3, two investigators uncovered the relationship of the disease hypercholesterolemia to low density lipoprotein (LDL) receptor genes--a discovery that has enabled them to begin to design new therapeutic approaches to treat this often fatal problem. The ultimate coupling of findings at the molecular level to effective clinical and epidemiological approaches will become more and more the way NIH-funded researchers develop arsenals of new dietary treatments.

The advances possible in all phases of research, including nutrition, are truly staggering. Researchers are working to make their vision of radically new, rationally designed therapies a reality. In the years ahead, the coming together of these research efforts will have a very deep impact on the health of the American people.

ACKNOWLEDGEMENTS

The Bureau, Institute, and Division (BID) representatives to the NIH Nutrition Coordinating Committee deserve special acknowledgement this year. The activities of the NCC would not be possible without the support and commitment to nutrition research of the members and alternates to this committee. The following people have devoted personal time and effort over and above their full-time BID responsibilities to make this Annual Report possible: Dr. Peter Greenwald, Dr. Ritva Butrum, and Dr. Carolyn Clifford, NCI; Nancy Ernst and Karen Donato, NHLBI; Dr. Joseph Ciardi, NIDR; Dr. Van Hubbard and Dr. Donald Murphy, NIDDK; Dr. Zekin Shakhashiri, NINDS; Dr. Daniel Mullally, NIAID; Dr. Yvonne Maddox, NIGMS; Dr. Ephraim Levin, NICHD; Dr. Barbara Underwood, NEI; Dr. Thorsten Fjellstedt and Dr. Michael Galvin, NIEHS; Dr. Ann Sorenson and Dr. Judith Hallfrisch, NIA; Dr. Stephen Heyse, NIAMS; Dr. Judith Vaitukaitis, Dr. Bernard Talbot, and Dr. Leslie Bullock, DRR; Dr. Joe Knapka, DRS; Dr. Kenneth Bridbord and Dr. Ferdinand Hui, FIC; Dr. Moira Shannon, NCNR; Gloria Stables, CC; Maureen Gardner, DLA; Dr. Ai Lien Wu, Dr. Sooja Kim and Dr. Donna Dean, DRG; Dr. Harold A. Schoolman, NLM; and Marc Stern, Office of Communications.

The timely publication of this report would not have been possible without the extraordinary cooperation and assistance of the many individuals from Editorial Operations Branch; Printing and Reproduction Branch, DTS, ORS; Medical Arts and Photography Branch, DRS; Administrative Office staff, OD; and many other people at the NIH who made special efforts for this report.

On behalf of the NCC members I wish to thank the staff of the Division of Nutrition Research Coordination (DNRC). Special thanks go to Dr. Betty Alford, Visiting Professor, and Dr. Darla Danford, Director, who accomplished the task of coordinating, writing, and overseeing production of this annual report despite impossible deadlines. Thanks are also due to Melissa Workman and Bronna Finn for data analysis and retrieval. I also wish to thank Ruth Preston, Lucille Wilfand, Margaret Murphy and Nancy Walther for their editorial assistance.

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William T. Friedewald, M.D.
Acting Chairman
Nutrition Coordinating Committee

MEMBERS OF THE NUTRITION COORDINATING COMMITTEE

(as of September 1, 1988)

NCC Acting Chairman: William T. Friedewald, M.D.
Staff Director: Darla E. Danford, M.P.H., D.Sc., R.D.
Executive Secretary: Bronna T. Finn

NCC Members

BID*	Member	Alternate
NCI	Daniel W. Nixon, M.D.	Ritva Butrum, Ph.D.
NHLBI	Nancy Ernst, M.S., R.D.	Barbara Dennis, Ph.D.
NIDR	Joseph E. Ciardi, Ph.D.	
NIDDK	Van S. Hubbard, M.D., Ph.D.	Donald G. Murphy, Ph.D.
NINCDS	Zekin Shakhashiri, M.D., M.S., M.P.H.	
NIAID	Daniel Mullally, M.D.	Dorothy D. Sogn, M.D.
NIGMS	Yvonne Maddox, Ph.D.	Leo von Euler, M.D.
NICHD	Ephraim Y. Levin, M.D.	
NEI	Barbara A. Underwood, Ph.D.	
NIEHS	Thorsten Fjellstedt, Ph.D.	
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NIAMS	Stephen P. Heyse, M.D., M.P.H.	Reva Lawrence, M.P.H.
DRR	Bernard Talbot, M.D., Ph.D.	Leslie Bullock, D.V.M.
DRS	Joseph J. Knapka, Ph.D.	
FIC	Kenneth Bridbord, M.D.	Ferdinand Hui, Ph.D.
NCNR	Moira Shannon, M.S.N., Ed.D.	

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* Bureau/Institute/Division

NCC Liaison Representatives

Organization	Member	Alternate
Clinical Center	Gloria Stables, M.S., R.D.	
Division of Computer Research and Technology	Judy Mahaffey	Arnold Pratt, M.D.
Division of Research Grants	Donna Dean, Ph.D.	Ai Lien Wu, Ph.D.
National Library of Medicine	Harold A. Schoolman, M.D.	
Division of Legislative Analysis	Christina Blakeslee	
Office of Communications	Marc Stern	
Nutrition Education Subcommittee	Karen Donato, M.S., R.D.	

DHHS NCC Liaison Representatives

Organization	Member	Alternate
Alcohol, Drug Abuse, and Mental Health Administration	Susan Blumenthal M.D.,M.P.A.	Ellen Stover, Ph.D.
Alcohol, Drug Abuse, and Mental Health Administration (Intramural)	Richard Veech, M.D.	Boris Tabakoff, Ph.D.
Centers for Disease Control	Frederick Trowbridge, M.D.	
Food and Drug Administration	John Vanderveen, Ph.D.	Lynn A. Larsen, Ph.D.
Health Resources and Services Administration	Elizabeth Brannon, M.S.,R.D.	Ann Prendergast, R.D., M.P.H.
National Center for Health Statistics	Catherine Woteki, Ph.D.	Carla Weinberg
Office of Disease Prevention and Health Promotion	Linda Meyers, Ph.D.	Marion Nestle, Ph.D.

USDA Liaison Representatives

USDA	Gerald Combs, Ph.D.	Suzanne Harris, Ph.D.

Other NCC Office Staff

Esperanza R. Briones, Ph.D.
Renee Cesara
Ruth Preston
Margaret Murphey
Lucillle Wilfand

MEMBERS OF THE NCC NUTRITION EDUCATION SUBCOMMITTEE

(as of September 1, 1988)

Cochairperson and Executive Secretary	Karen Donato, M.S., R.D. Nutrition Coordinating Committee Office
Cochairperson	Esperanza R. Briones, Ph.D.
Special Consultant	Nancy Ernst, M.S., R.D. National Heart, Lung, and Blood Institute
MEMBERS	
National Cancer Institute	Ritva Butrum, Ph.D. Luise Light, Ph.D.
National Heart, Lung, and Blood Institute	Marilyn Farrand, M.S., R.D.
National Institute of Diabetes and Digestive and Kidney Diseases	Van S. Hubbard, M.D., Ph.D.
Division of Research Resources	C. Alan Moore
Clinical Center	Gloria Stables, M. S., R.D.
Office of Communications	Don Ralbovsky

Section 1. Advances in Biomedical Nutrition Research and Training

THE NIH

The mission of the NIH is to improve the health of the nation by increasing the understanding of processes underlying human health, disability, and disease; advancing knowledge concerning the health effects of interactions between man and the environment; and developing and improving methods of preventing, detecting, diagnosing, and treating disease. To carry out its mission and legislative mandates, the NIH is organized into an Office of the Director (OD), 12 research institutes, one research division (the Division of Research Resources), three service divisions, and the National Library of Medicine. The organization also includes the Clinical Center, the Fogarty International Center, and the newly established National Center for Nursing Research. Figure I shows the components of the NIH. Through these components, the NIH is the major agency within the Federal Government that supports research and training in nutrition as it relates to health maintenance, disease treatment and prevention, and human development throughout the life cycle.

LEGISLATIVE BASE

The basic legislative authorities underlying all NIH activities are contained in the Public Health Service (PHS) Act. That act, primarily through provisions in Titles III and IV, authorizes all NIH-sponsored research, including both intramural and extramural programs; research training; information dissemination; health promotion and disease prevention activities; clinical studies and associated patient treatment; and NIH participation in cooperative research-related endeavors with other countries and in the training of foreign scientists. The legislative authority for nutrition at the NIH is presented in appendix A.

DIVISION OF NUTRITION RESEARCH COORDINATION

In May 1988, the Division of Nutrition Research Coordination (DNRC) was created within the Office of Disease Prevention (ODP) in the Office of the Director, as shown in figure 2. The creation of the new Division both firmly established the trans-NIH coordination of nutrition research and training as a permanent and identifiable position within the NIH and recognized the additional responsibilities acquired over time by the Nutrition Coordinating Committee (NCC) office. The current functions and responsibilities of the NCC are encompassed within this new framework. The DNRC and its NCC participate in three major categories of activity:

- Coordinated trans-NIH activities;
- Collaborative interagency activities at the DHHS level;
- Collaborative interagency activities at the Federal level.

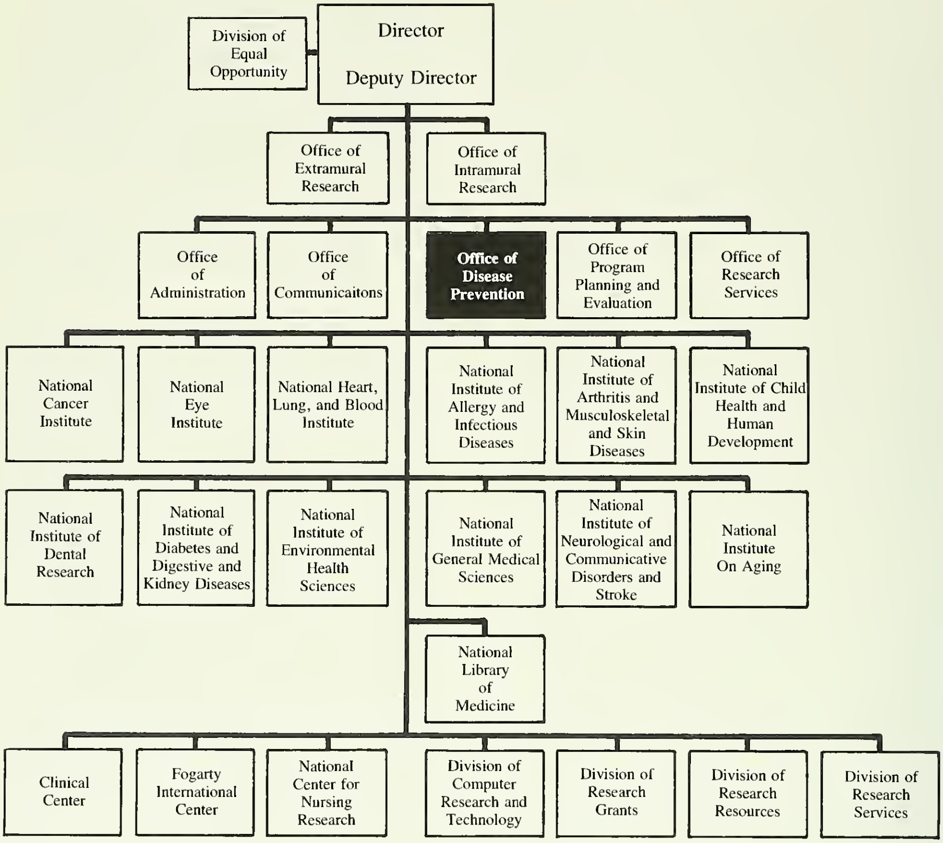
Coordinated Trans-NIH Activities

Nutrition Coordinating Committee and Subcommittees. In response to the recognition of the importance of nutrition, which had been identified as a "major priority area within the Department," and the need perceived by the NIH for better coordination of this trans-NIH research area, the NCC was established in the Office of the Director, NIH. It met for the first time in July 1975. Since that date, the NCC has operated as an NIH-wide forum and locus for the coordination of nutrition activities, helping the NIH to avoid duplication of effort and to speak with one voice on nutrition research matters. In 1977, the Committee developed a common definition of nutrition research at NIH (see table 1).

The NCC, which generally meets once per month, consists of representatives from 12 institutes, 2 divisions, and 2 centers. Additional NIH offices and other agencies of the DHHS and the U.S. Department of Agriculture (USDA) have liaison representatives to the committee. As of September 30, 1989, the NCC was composed of the chairman and 47 members, alternates, and liaison representatives (see listing on pages ix and x).

The mandate of the NCC, first published in 1977, is to review, stimulate, and encourage the necessary support of nutrition research and training in order to better define the role of nutrition in the promotion and maintenance of health and in the prevention and treatment of disease. A description of related NIH-wide

Figure 1. Components of the National Institutes of Health


Division of Equal Opportunity
Director
Deputy Director
Office of Extramural Research
Office of Intramural Research
Office of Administration
Office of Communicaitons
Office of Disease Prevention
Office of Program Planning and Evaluation
Office of Research Services
National Cancer Institute
National Eye Institute
National Heart, Lung, and Blood Institute
National Institute of Allergy and Infectious Diseases
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Child Health and Human Development
National Institute of Dental Research
National Institute of Diabetes and Digestive and Kidney Diseases
National Institute of Environmental Health Sciences
National Institute of General Medical Sciences
National Institute of Neurological and Communicative Disorders and Stroke
National Institute On Aging
National Library of Medicine
Clinical Center
Fogarty International Center
National Center for Nursing Research
Division of Computer Research and Technology
Division of Research Grants
Division of Research Resources
Division of Research Services

activities constitutes this *12th Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training, Fiscal Year 1988* (NIH Publication 89-2092, 1989). This publication has been produced by the Committee each year since 1977.

In addition to the regular business conducted at NCC monthly meetings, research scientists and representatives of professional groups frequently make special presentations on subjects of current interest to NCC members. These scientists may include NIH grantees from the academic community, as well as intramural or extramural investigators from NIH or other Federal agencies. (Appendix B shows seminars sponsored by the NCC during their monthly meetings for fiscal year 1988.)

Basically, the NCC provides a locus for the review and coordination of research and training efforts related to nutrition and for the development of the NIH Program in Biomedical and Behavioral Nutrition Research and Training. These activities minimize the duplication of effort among the institutes and identify areas where research, research training, and research manpower development need to be enhanced. This is accomplished through several different approaches, including the coordination of the development of program announcements (PAs), requests for applications (RFAs), and requests for proposals (RFPs), either sponsored jointly by several institutes or by an individual institute. (Appendix C shows PAs, RFAs, and RFPs in nutrition published in 1988.)

Table 1. Definition of Nutrition Research at the NIH

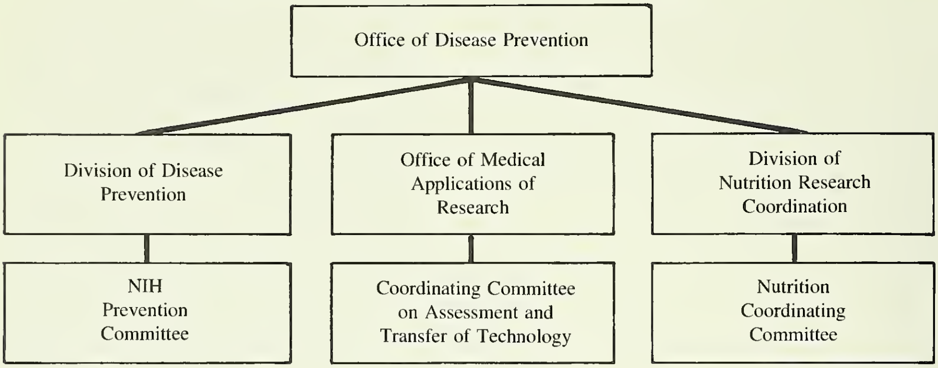
The term nutrition research includes studies designed to assess the consequences of food or nutrient intake and utilization in the intact organism, including humans, and the metabolic and behavioral mechanisms involved. These studies encompass investigation of nutrient variables at the cellular or subcellular level. This definition also includes:

- Research designed to elucidate the metabolic role or function of nutrients in both animal models and humans.
- All studies concerned with genetic-nutrient-environmental interactions where a nutrient is a variable.
- Dietary studies expected to produce significant changes in health status, including the maintenance of health and the treatment of disease in humans. Such studies might include clinical trials, epidemiological studies, metabolic studies, surveillance, and nutritional status monitoring studies.

The Committee plays a key role in the development of nutrition research policy at the NIH (see NIH Publication No. 86-2092). Currently, nutrition research policy at the NIH highlights eight areas. Research is emphasized in four of these topics: clinical nutrition throughout the life cycle, and nutritional factors in the development of disease, prevention of disease, and treatment of disease. The other four areas are related to education and technology transfer: the transfer of modern nutrition technology, nutrition education for professionals and the public, nutrition research training and research manpower development in nutrition, and trans-NIH and interagency coordination. The DNRC and its NCC also prepare and review many trans-NIH and interagency nutrition-related documents. In addition, they sponsor major conferences or workshops in nutrition, which are shown for 1988 in appendix D.The NCC/DNRC also periodically publishes the pamphlet *Nutrition Research at the NIH* (NIH Publication No. 90-2611, 1990). This booklet describes nutrition-related biomedical research programs at NIH, as they relate to the research and research missions of the various NIH institutes and divisions. Its content is intended to assist extramural investigators and other persons who wish to apply for grants and other agency funding.

The NIH liaison representatives offer a variety of assistance to the NCC. The representative from the Warren Grant Magnuson Clinical Center provides information on the nutrition-related clinical research conducted in this center. The liaison person from the Division of Computer Research and Technology designed and implemented the Human Nutrition Research and Information Management (HNRIM) System, which is operated by the DNRC. From the Division of Legislative Analysis, OD, the staff member provides the Committee with a mechanism for receiving, reviewing, and distributing information on proposed legislation affecting biomedical nutrition research and training. The staff member from the Division of Research Grants (DRG), who is Executive Secretary to the Nutrition Study Section, provides information on the number and types of nutrition-related applications submitted to the DRG, and offers insight into new review mechanisms and policies. The representative from the National Library of Medicine (NLM) provides information on the organization and access to scientific information related to nutrition and other biomedical sciences. The representative from the Office of Communications, OD, assists the NCC by referring questions from the media on nutrition-related topics to appropriate programs throughout NIH.

Figure 2. Components of the Office of Disease Prevention


Office of Disease Prevention
Division of Disease Prevention
Office of Medical Applications of Research
Division of Nutrition Research Coordination
NIH Prevention Committee
Coordinating Committee on Assessment and Transfer of Technology
Nutrition Coordinating Committee

Nutrition Education Subcommittee. Many activities of the Nutrition Education Subcommittee (NES) involve the transfer of the latest scientific information on various areas of nutrition research to members of the scientific community, the Congress, and the general public. Table 2 shows the mandate of the NES. During FY 1988, the NES reviewed NIH nutrition education publications written for the public to assure institute-wide scientific accuracy and consistency in providing dietary guidance information (see appendix E for review procedures and listing of publications). During FY 1988, the Subcommittee was extensively involved in reviewing *The Surgeon General's Report on Nutrition and Health*, which was published in July 1988.

Collaborative Interagency Activities at the DHHS Level

Nutrition Policy Board. The NIH is represented by the ODP and the DNRC on the DHHS Nutrition Policy Board (NPB) and its Dietary Guidance Subcommittee. The NPB consists of representatives of the PHS and other DHHS agencies involved in nutrition activities; it is chaired by the Deputy Assistant Secretary for Health.

A major activity of the NPB was the publication of a comprehensive analysis of the relationship between dietary factors and chronic disease risk. *The Surgeon General's Report on Nutrition and Health* summarized research on the role of diet in health and implications for dietary guidance, programs and services, and research and surveillance. The Report noted: "Its findings indicate the great importance of diet to health. They demonstrate that changes in present dietary practices of Americans could produce substantial gains in the health of the population."

Nine institutes of the NIH had primary responsibility for 14 of its 19 chapters. The chapters involved were "Coronary Heart Disease" and "High Blood Pressure" (NHLBI); "Cancer" (NCI); "Diabetes," "Obesity," "Kidney Diseases," "Gastrointestinal Diseases," and "Anemia" (NIDDK); "Skeletal Diseases" (NIAMS and NIDDK); "Dental Diseases" (NIDR); "Maternal and Child Nutrition (NICHD); "Infections and Immunity" (NIAID); "Neurologic Disorders" (NINCDS); and "Aging" (NIA). All of the institutes and the DNRC were involved in reviewing the entire report.

The NPB Subcommittee on Dietary Guidance coordinates DHHS activities that offer dietary guidance information geared to the healthy American population, including ensuring Departmental consistency with the principles established in the *Dietary Guidelines for Americans;* coordinating DHHS portions on dietary guidance; facilitating consistency in dietary guidance from all Federal sources; and exchanging information on ways to improve the effectiveness of dietary guidance publications.

Table 2. Mandate of the NCC Nutrition Education Subcommittee

- To review all NIH nutrition publications and other educational materials destined for the public to assure scientific accuracy and consistency across the institutes in providing dietary guidance information.
- To identify mechanisms to improve nutrition education activities related to professional as well as public education.
- To initiate, develop, or review nutrition education activities or programs directed to NIH employees--particularly those to commemorate National Nutrition Month.
- To serve as advisors to consider nutrition-related issues, programs, or publications of other Government agencies or departments when pertinent to the interests of the NIH and requested by the NCC, by the Director, Office of Disease Prevention, or by both.

DHHS Task Force on the Nutrition Objectives for the Nation. The NIH is represented by DNRC on the DHHS Task Force on the Year 2000 National Health Objectives. The inclusion of nutrition as a separate priority in the 1990 Health Objectives for the Nation reflected the growing consensus about the role of nutrition in health promotion and disease prevention. In August 1989, the NIH was co-lead with the Food and Drug Administration (FDA) for the nutrition priority area of the Year 2000 National Health Objectives. The Year 2000 Health Objectives for the Nation will be published in the summer of 1990. The Year 2000 project builds upon the 1990 objectives in several substantive ways. It expands the range of priorities into new areas, such as acquired immunodeficiency syndrome (AIDS), and expands the focus of others, such as high blood cholesterol and high blood pressure. The project targets populations that are at high risk and are especially hard to reach; it also identifies settings such as the workplace, which are conducive to a variety of disease prevention and health promotion interventions. The problems of particular groups are addressed such as those of Native Americans, blacks, Hispanics, and older Americans. Nutrition is a crosscutting research area involved in many of the 21 priority topics for 2000 such as those aimed at improving maternal and child health; preventing and controlling high blood cholesterol and high blood pressure; and maintaining the health and quality of life of older people.

Collaborative Interagency Activities at the Federal Level

Interagency Committee on Human Nutrition Research. Nutrition research is coordinated at the Federal level through the Interagency Committee on Human Nutrition Research (ICHNR). The DNRC, NIH, serves as Executive Secretariat to the ICHNR. The ICHNR is cochaired by the Assistant Secretary for Health, DHHS, and the Assistant Secretary for Science and Education, USDA. It comprises representatives from the Office of Science and Technology Policy (OSTP) in the Executive Office of the President, the Department of Commerce-National Oceanic and Atmospheric Administration (DOC-NOAA), the Department of Defense (DOD), the Agency for International Development (AID), the National Science Foundation (NSF), the Veterans Administration (VA), and the National Aeronautics and Space Administration (NASA), in addition to DHHS and USDA agencies.

The ICHNR fosters communication among research agencies and currently has four active subcommittees:

- Subcommittee on Nutrition Research and the RDAs. This subcommittee has responsibility for identifying scientific issues that are relevant for agency research emphasis as well as research areas relevant for setting the recommended dietary allowances (RDAs). The NIH chairs this Subcommittee.
- Subcommittee on Technology, Nutrition, and Food Production. A standing subcommittee chaired by the Assistant Secretary for Science and Education, USDA, this subcommittee was formed to

monitor scientific, regulatory, and marketing developments with implications for the food supply.

- Subcommittee on Nutrition Monitoring Research. This subcommittee was formed to provide interagency coordination for the National Nutrition Monitoring System (NNMS) research, with cochairs from the Offices of the Assistant Secretaries for Health, DHHS, and for Food and Consumer Services, USDA. This subcommittee serves as the interface between the Interagency Committee on Human Nutrition Research and the Interagency Committee on Nutrition Montoring. NIH is represented on this subcommittee as a major funder of NHANES and a related research user of nutrition monitoring research data.
- Subcommittee on the Biennial Conference for Federally-Supported Human Nutrition Research Units and Centers. This subcommittee organizes and sponsors this interagency biennial meeting, which serves as a forum for information exchange and a stimulus for research collaboration among agencies. The NIH chairs the program planning subcommittee. The fourth conference was held February 15-16, 1989, at the Lister Hill Auditorium at the NIH. This year it addressed two topics of special interest to Federal nutrition researchers: "Nutritional Function" and "Nutrient Interactions and Toxicities." The scientific speakers were from the NIH-supported Clinical Nutrition Research Units (CNRUs), ARS-supported Human Nutrition Research Centers (HNRCs), Human Nutrition Information Service (HNIS) researchers from USDA, several VA laboratories, NASA, DOD, AID, and FDA.

Interagency Fish Oil Test Materials Program. The Interagency Fish Oil Test Materials Program was formally initiated in 1986 by the signing of a memorandum of understanding (MOU) between the NIH; the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA); and the DOC-NOAA. Under the MOU, it was agreed that the NIH, ADAMHA, and DOC-NOAA would cooperate on, and provide support to, research activities related to establishing and clarifying the biological mechanisms by which a seafood diet or the ingestion of fish oils which include omega-3 (n-3) fatty acids, may influence health and modulate a number of human disease processes.

The purpose of this program is to provide a consistent supply of quality-assured/quality-controlled test materials to researchers in order to encourage high-quality research and to facilitate the evaluation of the role that omega-3 fatty acids have in human health and disease. To fulfill this purpose, NOAA completed, during the summer of 1987, construction of a pilot plant in Charleston, South Carolina, which is now producing fish oil test materials, including n-3 ethyl ester concentrate, ethyl esters of olive oil, encapsulated purified steam-deodorized menhaden oil with and without antioxidants, and antioxidant-balanced controls. These test materials are provided free of charge to qualified NIH and ADAMHA grantees, intramural scientists, and independent researchers funded by other peer-reviewed sources (NIH Guide for Grants and Contracts: 17(5)Feb. 12, 1988).

The program is administered through the DNRC by a Fish Oil Test Materials Advisory Committee (FOTMAC) with membership from scientists representing the funding agencies (NIH and ADAMHA), the research community, the DOC and the FDA. The FOTMAC is cochaired by scientific staff from the NIH and ADAMHA.

The Human Nutrition Research and Information Management System. The Human Nutrition Research and Information Management (HNRIM) System under the aegis of the ICHNR was established and housed in the NCC office in 1982. The system, now in its seventh year of operation, is maintained in the DNRC, under the auspices of the ICHNR. It is a computerized data base and data retrieval system that contains information on nutrition research and research training activities supported by the Federal government. The data base contains approximately 4,000 projects for each fiscal year, and includes the following types of information: sponsoring organization, project identifier numbers, project title, principal investigator, organization name, address, nutrition classification categories, project abstract, percent related to nutrition, fiscal year, and start date. Appendix F includes the nutrition classification system used in the HNRIM system.

The HNRIM system database was developed in accordance with the National Agricultural

Research, Extension, and Teaching Policy Act of 1977 (7 USC 3177). Participating agencies include DHHS, USDA, VA, AID, DOD, and DOC-NOAA. In July 1986, the system was made available to the public for purchase through the National Technical Information Service (NTIS) of DOC.

Interagency Committee on Nutrition Monitoring. This interagency Committee, the Interagency Committee on Nutrition Monitoring (ICNM), was formed in July 1988 to improve the effectiveness of the National Nutrition Monitoring System (NNMS), which includes all federally-supported or conducted surveys on human nutrition and food consumption and surveillance of the food supply. The ICNM is cochaired by the Assistant Secretary for Health, DHHS, and the Assistant Secretary for Food and Consumer Services, USDA. Its membership includes representatives from the DHHS (NIH, FDA, CDC) and USDA (Human Nutrition Information Service, Agriculture Research Service, Food and Nutrition Service, Economic Research Service) as well as Agency for International Development, Bureau of the Census, Bureau of Labor Statistics, Army Institute of Environmental Medicine/DOD, and Veterans Administration.

The ICNM has three active working groups:

- Survey Complementarity. This group helps the Committee work towards its goal of integrating existing Federal surveys and surveillance activities into a network that will provide a better picture of both total population and special subgroup nutritional health. Federal and state relations will be a special focus.
- Information Dissemination and Exchange. This group assists the Committee in improving communication with users of nutrition monitoring data and in becoming more responsive to their needs. The goal is to provide a dynamic information exchange process between data users and those who generate data.
- Food Composition Data. This group monitors the availability of food composition data for use in the System, and identifies food composition data need. It also proposes options to improve the utility of such data, and to facilitate appropriate coordination among member agencies.

A second progress report on nutrition monitoring in the United States, to be submitted to Congress in 1989, is in press. For this report, the DNRC, NIH, participated with other representatives from DHHS and USDA agencies in the DHHS Joint Project Steering Committee initiated in 1987. A directory of nutrition monitoring activities, in whose development NIH participated, will also be issued in 1989.

USDA/DHHS Nutrition Education Committee for Maternal and Child Nutrition Publications. This Committee provides a systematic mechanism for staff representing various agencies within the USDA and the DHHS to exchange information on their progress and plans related to maternal and child nutrition education. In addition to reviewing publications in developmental stages to assure consistency of content, the Committee has stimulated greater collaboration on joint projects and wider dissemination of information on nutrition education. It is cochaired by USDA, and DHHS. Members include a representative from the Nutrition and Technical Services Division and the Supplemental Food Programs Division, Food and Nutrition Service; the Nutrition Education Division, Human Nutrition Information Service; the Home Economics and Human Nutrition Extension Service; and the Food and Nutrition Information Center, National Agricultural Library. For the DHHS, individual representatives are from the Bureau of Maternal and Child Health and Resources Development, Health Resources and Services Administration; the Nutrition and Dietetics Section, Indian Health Service; and the DNRC, NIH.

For additional information on the DNRC, NCC, and related activities, contact:

Darla E. Danford, M.P.H., D.Sc., R.D.
Director
Division of Nutrition Research Coordination
Building 31, Room 4B63
National Institutes of Health
Bethesda, MD 20892
(301) 496-9281

Section 2.

Reports of Participating Bureaus, Institutes, and Divisions: NIH Nutrition Coordinating Committee Members

REPORTS OF PARTICIPATING INSTITUTES, DIVISIONS, AND CENTERS: NIH NUTRITION COORDINATING COMMITTEE MEMBERS

Each of the 12 NIH institutes supports various aspects of nutrition research relevant to its particular research mission. Historically, the research and training focus of the bureaus, institutes, and divisions (BIDs) of the NIH has changed as technology has progressed and as the science base needs of the research community have evolved. Together, the research missions of the 12 institutes, 2 divisions, and 2 centers outlined here cover the disease conditions that are a major threat to the health and well-being of the American population.

The acquisition of new biomedical knowledge is a serendipitous process; it is difficult to know where or how new knowledge gained will be applied to specific human diseases. Further, areas of scientific interest do not readily lend themselves to sharp lines of demarcation. For example, research on osteoporosis supported by the NIAMS has relevance to the NIA as well, and the reverse is also true. For this reason, the NIH program in biomedical and behavioral nutrition research and training is greater than the sum of the individual contributions of the NIH institutes, divisions, and centers that are described in this section. Indeed, ensuring this synergy is a vital task of the NCC. Therefore, the individual descriptions that follow are not meant to be absolute but rather to demonstrate the depth and breadth of NIH's commitment to the field of nutrition.

Cancer is the second leading cause of death in the United States with more than 475,000 persons in 1987 dying from this disease. Also, in the same period, more than 900,000 new cases of cancer occurred.

Since the NCI was established in 1937, scientists have identified various cancer-causing factors in the environment and research leaders have sought to reduce the exposure of the population to those risk elements. Research and training at NCI are carried out by both intramural and extramural programs of the Division of Cancer Prevention and Control, the Division of Cancer Treatment, the Division of Cancer Etiology, and the Division of Cancer Biology and Diagnosis.

Since the establishment of the Cancer Prevention Research Program (CPRP) by the Division of Cancer Prevention and Control in 1982, a coherent cancer prevention research plan, focused on nutrition, has been developed. This program has both intramural and extramural components which, when interacting with other NCI divisions and programs, allows prevention strategies to flow efficiently from the laboratory to the clinic. The intramural components of the CPRP are the Cancer Prevention Studies Branch and the Cancer Nutrition Laboratory; the extramural components are the Chemoprevention Branch, the Diet and Cancer Branch, and the new Cancer Prevention Clinical Trials Branch.

PROGRAM HIGHLIGHTS

NCI nutrition research is conducted with a variety of approaches: through epidemiologic studies of various population groups with distinctive food preparation and consumption patterns, by clinical evaluations of dietary interventions, in laboratory studies of food content and components, and with biochemical/physiologic assessment of nutrient metabolism and absorption patterns in animals and humans.

A number of epidemiologic and experimental studies suggest that about 35 percent of cancer deaths may be related to dietary factors. Protection against certain types of cancer may be related, for example, to certain micronutrients such as vitamins C, E, B_6 and folic acid, trace minerals such as selenium, or perhaps certain carotenoids such as beta-carotene. A number of epidemiologic studies and clinical trials are now under way to determine the potential role of these agents in reducing cancer risk.

Diets high in total fat are associated with cancers of the breast, colon, uterus (endometrium), prostate, and ovary. High intake of dietary fiber, on the other hand, may be associated with a reduced risk of colorectal cancer.

The CPRP in the Division of Cancer Prevention and Control seeks to identify ways to reduce the incidence or progression of cancer through applied intramural and extramural research in the areas of diet and nutrition and through chemoprevention. Research efforts in diet and nutrition focus on identifying dietary factors that inhibit the initiation or promotion of cancer. Studies and activities related to these factors include investigations of the metabolism of nutrients; the role of various nutrients and dietary components in causing and preventing cancer; the interaction of genetic, nutrient, and environmental factors in the initiation or progression of cancer; the nutrient content of various foods; the identification of determinants of dietary practices and development of methods to modify dietary practices; and the testing of hypotheses in dietary intervention clinical trials.

In 1988, a new intramural Laboratory for Nutrition and Cancer Research was established by the Division at the Frederick Cancer Research Facility in Frederick, Maryland. This intramural nutrition laboratory will focus on three major cancer prevention areas: basic nutrition research, nutritional epidemiology, and clinical/metabolic nutrition research. In addition, facilities have been identified at the NIH Clinical Center for conducting body composition and nutrient metabolism studies, and for controlled feeding studies.

Today, chemoprevention of cancer occupies a key position as a research strategy both at NCI and among the many collaborating institutions throughout the world. To discover new innovative chemoprevention approaches, NCI each year selects synthetic or natural micronutrients and other low molecular weight substances to be assessed either by investigations using experimental animals or through epidemiologic studies or clinical evaluation.

The nutrition program in the Division of Cancer Treatment deals mainly with nutritional problems, including cancer cachexia, or wasting, which may arise in the course of chemotherapy. Poor prognosis of cancer patients is often associated with altered nutritional status. Anorexia, another symptom of cancer patients, may interfere with both the treatment and the patient's sense of comfort. Promising therapies are tested to aid in stabilizing the weight of cancer patients. Metabolic changes in cancer patients that provoke neurochemical and biochemical events causing anorexia are being studied to provide new information on how these events may be modified. A clinical study is under way to determine the effect of folacin status on frequency of chemotherapy-induced chromosomal alterations and somatic mutations in patients with malignancies, leukemia, and breast cancer.

Epidemiologic and experimental studies in the Division of Cancer Etiology continue to provide evidence that dietary factors contribute to a substantial proportion of human cancer. Variations among countries in cancer incidence and mortality rates suggest a significant role for dietary and nutritional factors; similar indications arise from migrant populations whose cancer rates, with increasing acculturation, resemble those of indigenous groups. An increasing number of case-control and cohort studies have found certain dietary patterns to be associated with specific cancers. Nonetheless, many dietary factors remain to be investigated, and the nutritional etiology of most cancers is yet to be resolved. Efforts to generate and test hypotheses in this area continue to be emphasized in the Division's intramural and extramural research program.

A large number of case-control and cohort studies are under way to examine the relationship of diet, specific foods, food groups, or nutrients to the incidence of cancer. Studies are being conducted in the U.S. and other countries to explore the effects of affluent diets, high in fat and calories, on the incidence of breast, prostate, colon, endometrial, and ovarian cancer; and the effects of diets low in vegetables and fruits on the incidence of lung, oral, esophageal, colorectal, and cervical cancer. The relationship between alcohol consumption and breast, oral-pharyngeal, and esophageal cancer is being evaluated.

RESEARCH DIRECTIONS

The NCI is giving substantial emphasis to nutrition in its programs to reduce mortality from cancer. The NCI supports extensive research on the relationship between nutrition and cancer in a wide variety of areas: prevention, epidemiology, etiology, basic cellular mechanisms, therapy, rehabilitation, research development, and information dissemination.

Among the many research approaches being pursued, the following are of particular note:

- Through epidemiological investigations, assessments are being made about the effects of diet and nutritional status on cancer incidence and survival. Dietary factors under investigation include food groups (e.g., vegetables and fruit) specific foods (e.g., coffee), cooking practices (e.g., frying at high temperatures), and individual dietary constituents (e.g., beta-carotene, vitamin C, folacin, fat, and dietary fiber). Nutritional parameters under investigation include plasma cholesterol, serum fatty acid profiles, and serum micronutrient levels. Studies are being conducted in low-risk populations such as Chinese and Japanese migrants to the U.S. who have low rates of breast cancer, and in high-risk populations, such as blacks who have high rates of prostate, pancreatic, lung, cervical, and esophageal cancers.
- Through chemoprevention and dietary clinical trials, studies are being carried out on the quantitative relationships between food, nutrient intake, and cancer incidence.
- Nutritive and nonnutritive dietary components (i.e., foods and food additives) are being assessed as possible carcinogens and procarcinogens, with attention being directed to interactions in carcinogen metabolism.
- Investigators are studying mechanisms by which nutrients affect *in vitro* tumor cell metabolism and growth, including the role of folacin in protein synthesis, the regulation of gene transcription by retinoids, the involvement of vitamin D_3 in inhibiting cell proliferation, the effect of essential fatty acids on colon tumor cell growth and metastasis, and the means by which chemotherapeutic agents alter cholesterol synthesis and cell membrane function.

- Methods of food preparation and processing, as well as ingestion of food and vitamin supplements, alcohol, fat, and fiber, are being appraised for a role in the promotion of cancer.
- Investigators are developing ways of measuring phytochemicals in fruits and vegetables and biological fluids, and assessing phytochemicals for their potential role in cancer prevention.
- The relationship between blood and tissue micronutrient levels is being examined.
- An international food component database is being developed to enhance the quality, quantity, and worldwide accessability of nutrient and nonnutrient data for research.
- The potential role of obesity and immune dysfunction in cancer risk is being explored through both epidemiologic and laboratory studies.
- Researchers are seeking nutritional agents that may serve in the chemoprevention of cancer and are developing methodologies to evaluate the cost-effectiveness of these prevention strategies.
- Accurate and reliable means of measuring human dietary intake are being generated.
- Suitable methods for assessing nutritional status, metabolic patterns, and genetic predisposition are being evaluated for use in epidemiological studies.

Clinical aspects of the care and management of cancer patients require focused nutrition research, not on cancer prevention, but on the effective treatment of cancer. Among such investigative studies are the following:

- Clinical trials are under way to evaluate the effectiveness of nutritional support in the rehabilitation of the cancer patient, nutrition requirements during remission, and nutrient and dietary factors needed to maximize patient survival.
- The nutritional requirements of the cancer patient and his or her neoplastic tissues are being appraised, with emphasis on nutrient uptake, utilization, and cellular control mechanisms in both normal and neoplastic tissues; and on host-tumor interactions and competition for nutrients. This research helps to develop a more complete understanding of tumor growth and differentiation as it affects the host's metabolism. Knowledge of growth requirements and control mechanisms helps to formulate new therapy schemes based on differential nutrient availability.
- In order to develop techniques and procedures to maintain or improve the nutritional status of the patient, various formulations and delivery systems in total parenteral and enteral nutrition and oral supplementation are being examined. Energy expenditures are also being measured using whole body calorimetry. Behavior modification procedures and pharmacological agents are used to improve the appetite of cancer patients. In addition, laboratory research is under way on the etiology of cachexia, or wasting, in cancer patients.
- Three Clinical Nutrition Research Units, each conducting an intensive program of nutrition research, are funded through the NCI.
- Educational materials and programs are being developed on the role of diet and nutrition in cancer etiology, prevention, treatment, and rehabilitation for dissemination to health care professionals and to the public.

OUTLOOK

Research leaders have concluded that controlled intervention trials, when feasible, represent an integral part of the effective bridge between basic knowledge and the application of research results to cancer prevention. Although costly and often complex, well-designed randomized, controlled trials can provide the most definitive evidence of the efficacy of an intervention for human populations. Multi-institution trials are often necessary to achieve an adequate number of trial participants. The new Cancer Prevention Clinical Trials Branch will stimulate and facilitate these trials.

For more information on the NCI nutrition program, contact:

Peter Greenwald, M.D.
Director
Division of Cancer Prevention and Control
National Cancer Institute
Building 31, Room 10A52
National Institutes of Health
Bethesda, MD 20892
(301) 496-6616

Coronary heart disease continues to be the leading cause of death in the U.S. More than 1.25 million heart attacks occur each year with over 500,000 deaths. High blood pressure (hypertension) occurs in almost 58 million people, including 39 million under age 65. In the years since NHLBI was established in 1948, its nutrition research program has been designed to help prevent three major diseases: heart disease, lung disorders, and blood diseases. With heart disease as the nation's number one killer, a large part of related research is focused on preventing heart attacks; lowering high blood pressure as well as high blood cholesterol; and reducing the incidence of atherosclerosis, or hardening of the arteries. The potential role of nutrition in the cause and prevention of sickle cell disease, respiratory distress syndrome, and pulmonary abnormalities is also under investigation.

The NHLBI's research and training program is administered through a variety of funding mechanisms. In its nutrition program as in other NHLBI research, the Institute's research efforts are focused in four extramural divisions: the Division of Heart and Vascular Diseases, the Division of Lung Diseases, the Division of Blood Diseases and Resources, and the Division of Epidemiology and Clinical Applications. Additional studies are conducted in the Intramural Division. The Office of Prevention, Education and Control is responsible for the development and dissemination of nutrition information and materials related to the risk factors for cardiovascular heart disease.

PROGRAM HIGHLIGHTS

To carry out its research goals, the NHLBI conducts its nutrition research across a broad spectrum, from biochemical studies of the cell and its DNA to clinical studies of dietary interventions aimed at reducing the risk of disease-related morbidity and fatality. Applied research, demonstration projects, public education, and research training programs are under way with the ultimate goal of improving the nutrition and health of the U.S. public.

Nutrition and Cardiovascular Health

Three NHLBI research programs are studying cardiovascular risk factors in children ages 8 years and up. One study focusing on children with elevated levels of LDL-cholesterol is a clinical intervention study called DISC (Dietary Intervention Study in Children). Following a successful feasibility phase which studied 146 children ages 8-10 years, the DISC Data and Safety Monitoring Committee gave approval to a full-scale trial to include 600 children. The trial will test the efficacy, acceptability, and safety of a fat-modified diet designed to lower blood LDL-cholesterol levels in children. Another study, the NHLBI Growth and Health Study (NGHS), is a 5-year observational study on 2,000 girls ages 9-10 years. The purpose of the study is to investigate racial differences in the onset and occurrence of obesity and other cardiovascular risk factors in black and white girls. Finally, 16,000 elementary school children beginning in the third grade will be studied in an NHLBI program called CATCH (Child and Adolescent Trial for Cardiovascular Health), which is currently in its feasibility phase. This study will assess whether changes in dietary choices and activity patterns of children will result from promotion efforts through school-based cardiovascular curricula, parental intervention programs, and major environmental changes, such as in the school lunch program.

Several NHLBI cardiovascular risk reduction research programs are under way on adults as well. These clinical studies are testing prevention and intervention strategies, many of which have nutritional components for preventing and treating hypertension.

International Cardiovascular Nutrition Research

The international research component of the Institute, operating under a series of bilateral agreements, is carrying out joint epidemiologic studies of cardiovascular and cardiopulmonary diseases in China and the Soviet Union.

Cardiovascular diseases are among the main causes of death in China. While coronary heart disease is still low in China, it is rising. The China study is a longitudinal study of risk factors in population samples of urban and rural adults in the north (Beijing) and south (Guangzhou). To date, baseline and one followup survey have been carried out. Cardiovascular disease risk factors are more prevalent in the north than in the south. For example, mean body weight is 7-10 kg higher in the north, hypertension rates are 3.6 times higher, mean serum cholesterol is about 180 in the north and in southern urban samples, and less than 160 in the rural south. Dietary intake of fat was 26 percent and 27 percent of energy in urban Beijing and Guangzhou samples, respectively, and 22 percent and 17 percent in respective rural samples. Subsequent dietary changes reflect an increase in consumption of animal fat, animal protein, and cholesterol.

The study in the USSR is part of the Lipid Research Clinics (LRC) Program. Two prevalence studies were carried out in samples of adult men and women in Moscow and Leningrad. The study is currently in the mortality followup phase. About 10 years of followup have been completed. The baseline average dietary pattern was about 39 percent (en) fat, and 16-17 percent (en) saturated fatty acids. Baseline data for women showed a high prevalence of obesity, higher than in US-LRC samples. Data are being analyzed with respect to this finding.

At baseline, HDL was strikingly higher in USSR-LRC men compared to US-LRC men. Initial mortality findings showed that HDL was positively related to non-CHD deaths but it was not related to CHD deaths in the Soviet sample. Currently, the data are being analyzed to determine the reasons for this seemingly anomalous finding.

These studies, because of the differences in prevalence of risk factors and rates of disease among three countries, are providing new insights in our understanding of the causes and sequelae of CHD.

National Cholesterol Education Program

The National Cholesterol Education Program (NCEP), launched in 1985, has recommended very specific guidelines for the detection, evaluation, and treatment of high blood cholesterol levels in adults through the issuance of the Adult Treatment Panel Report. This patient-based approach seeks to identify individuals at high-risk who will benefit from intensive intervention efforts. Dietary modification is the cornerstone to the treatment plan. In FY 1988, the Population-Based Panel was convened to examine the scientific evidence and make recommendations for the population-based approach that seeks to lower the mean serum cholesterol level by modifying the dietary habits of the entire population. This strategy compliments the high risk strategy in its attempts to lower blood cholesterol levels and thereby help prevent coronary heart disease. The issue of screening is also being addressed by the panel since it may serve an important role as an interface between the population and patient-based approach and may also help to motivate the public to make dietary changes. The recommendations of the Population-Based Panel will be released in late 1989 or early 1990.

The issue of blood cholesterol levels in children and adolescents is being considered by an expert panel. This expert panel will consider the available scientific evidence, identify important issues to address and make recommendations to physicians and other health and education professionals. Issues of interest include the age range(s) to which the recommendations apply, risk classification of cholesterol levels, dietary changes — for whom; at what levels of blood cholesterol; and goal blood cholesterol levels. This panel's recommendations are expected to be released in June 1990.

The NCEP has produced a number of educational materials for health professionals and patients based on the Adult Treatment Panel Report. These include *Eating To Lower Your High Blood Cholesterol* and *So You Have High Blood Cholesterol*, brochures which were awarded a first prize by the National Association of Government Communicators; *A Community Guide for Cholesterol Resources*; a physician's kit on the treatment of high blood cholesterol which includes the patient brochures and was distributed to primary care physicians across the country; a continuing medical education monograph for physicians entitled *Cholesterol: Current Concepts for Clinicians*; and a dietitian's kit entitled *Keep In Step With The Treatment of High Blood Cholesterol* which will be distributed to over 20,000 dietitians with the assistance of the American Dietetic Association.

National High Blood Pressure Education Program

Since 1972, the National High Blood Pressure Education Program (NHBPEP) has released four joint national committee reports on the detection, evaluation, and treatment of high blood pressure. The fourth report, released in 1988, includes a greater emphasis on the role of nonpharmacologic therapy, particularly weight reduction, sodium restriction and moderation of alcohol consumption, in lowering elevated blood pressure and improving the efficacy of pharmacologic agents. Nonpharmacologic approaches are recommended as the first step in therapy and as an adjunct to pharmacologic therapy. Because of the clear relationship between obesity and blood pressure, weight control to within 15 percent of desirable body weight is recommended for all obese hypertensives. Since excessive alcohol intake may lead to elevated blood pressure, poor adherence to antihypertensive therapy and occasionally refractory hypertension, alcohol should be limited to no more than 1 ounce of ethanol daily. A high sodium intake plays a critical role in maintaining the elevated blood pressure of some hypertensive patients and in limiting the effectiveness of certain antihypertensive drugs. Thus, sodium intake is restricted to 70 to 100 mEqs or 1.5 to 2.5 grams of sodium per day. The possible role of calcium, potassium and polyunsaturated fats, especially in the form of fish and fish oils, in blood pressure control are also discussed in the report.

The National Heart, Lung, and Blood Institute joined forces with the National Cancer Institute in developing *Eating for Life*, a publication that discusses food choices and eating patterns that may help reduce both the risk for developing cardiovascular disease (CVD) and some types of cancer. The focus on heart disease covers those dietary changes within the Dietary Guidelines for Americans that are needed to help reduce high blood cholesterol and high blood pressure, two of the major CVD risk factors. Tips for grocery shopping, preparing foods, eating out, and better mealtime choices are included in the pamphlet.

RESEARCH DIRECTIONS

In its nutrition program as in other NHLBI research, the Institute's prevention efforts are targeted toward heart and vascular diseases, lung diseases, and blood diseases and resources. The following are examples of research supported by the NHLBI:

Heart and Vascular Diseases

- Identify mechanisms by which nutrients and other dietary factors influence blood pressure both under normal conditions and with hypertension.
- Explore the role of nutrition in intervention studies of cardiovascular disease risk.
- Conduct studies to determine racial, ethnic, and female differences in CHD including metabolism, risk factors, and diet responsiveness.
- Identify behavioral determinants of food consumption patterns and nutrient intake in relation to the risk of disease and the promotion of health.
- Improve the measurement of diet and nutrient intake, including acquisition of food composition data and development of automated methods of assessing dietary intake of individuals.
- Develop effective nutrition education strategies, methods, and materials for the dissemination of information on nutrition and disease prevention to health professionals and to the public in schools, work sites, clinics, and communities.
- Support training in nutrition as it relates to heart and vascular diseases.
- Elucidate the role of body weight and diet in cardiovascular disease and its risk factors.
- Continue surveillance of public knowledge and physician practices that pertain to diet and cardiovascular disease.

Lung Diseases

- Improve the understanding of the effects of nutritional status on immune defense functions in the developing and adult lung; the effects of malnutrition on normal resistance to pulmonary infections; and the role of nutritional factors in the development of bronchopulmonary dysplasia
- Explore the role of nutrition in preventing respiratory muscle dysfunction in acute and chronic pulmonary disease.
- Support studies on the role of various nutrients on nonrespiratory lung functions such as the synthesis and metabolism of surfactant and prostaglandins.
- Determine the effect of dietary factors on the central control of breathing and on neurophysiology within the lung and airway tissues.
- Investigate the role of specific nutrients in adult and infant respiratory distress syndromes and in other forms of respiratory failure.

- Support training in nutrition as it relates to lung diseases.

Blood Diseases and Resources

- Identify mechanism(s) by which nutrients and other dietary factors influence the blood-clotting function of platelets.
- Elucidate the role of nutrients and other dietary factors in the genesis, treatment, and prevention of blood vessel obstruction.
- Continue research on energy balance and nutrient requirements among children with sickle cell disease, especially children who fail to thrive and adolescents who are in the rapid growth phase.
- Determine the time of appearance and the intensity of nutritional abnormalities in sickle cell patients.
- Conduct studies on the benefits of appropriate dietary intervention and nutritional supplementation on growth and development, and on the morbidity of children with sickle cell disease.
- Improve understanding of nutritional factors in the management and clinical variability of sickle cell anemia.
- Characterize the relationship of nutritional deficiencies and immune dysfunction in sickle cell disease.
- Support training in nutrition as it relates to blood diseases and resources.
- Elucidate the role of nutrients and other dietary factors on the genesis and treatment of high blood pressure.
- Support research in nutrition education for medical students and for physicians in their private practice.
- Continue to support research to improve assessment and control of diet in research studies.

OUTLOOK

The NHLBI seeks to meet its goals of better health for the American people through research leading to improved diagnosis, treatment, and prevention of heart, vascular, lung, and blood diseases. The Institute's nutrition research program is a key element in this effort.

Surgeon General C. Everett Koop noted in his July 1988 "Report on Nutrition and Health" that Americans are already making dietary changes, as witnessed by the shift to products lower in saturated fats. It is NHLBI's objective to extend the gains already made in national eating behaviors by applying research strategies and technology to nutrition, thereby reducing the premature death rate from cardiovascular, pulmonary, and blood diseases.

For more information on the NHLBI nutrition program, contact:

Nancy Ernst, M.S., R.D.
Nutrition Coordinator
National Heart, Lung, and Blood Institute
Federal Building, Room 212
National Institutes of Health
Bethesda, MD 20892
(301) 496-2533

The NIDR is the primary sponsor of dental research and related training in the U.S. Its mission is to support studies to establish the causes, to develop better treatments, and ultimately to find ways to prevent or substantially lower the risk of developing oral disease. Congressional action in 1948 established NIDR as one of the National Institutes of Health. The forerunner of NIDR was the Dental Hygiene Unit, created in 1931 at the then newly formed National Institute of Health. Early research by this unit ultimately resulted in fluoridation of community water supplies as a safe and effective means of reducing dental caries.

Institute scientists, as well as those affiliated with grant-supported NIDR programs, have made encouraging progress in improving the nation's oral health through advances in diagnosis, treatment, and prevention. The Institute has organized its efforts into three major components: the Extramural Program; the Intramural Research Program centered in NIDR's own laboratories and clinics in Bethesda; and the Epidemiology and Oral Disease Prevention Program. The latter, the newest organizational unit of the NIDR, sponsors epidemiologic studies of oral disease and engages in controlled clinical trials of potential preventive agents and regimens, promoting their dissemination to the dental profession and the general public. Together, the three organizational divisions of the NIDR cover 14 areas of oral health research, including nutrition.

PROGRAM HIGHLIGHTS

Impressive gains in oral health have been made which can be attributed to a variety of preventive measures, some as a result of an increased appreciation of the influence of diet and nutrition. The successes are not complete, however. Dental caries and periodontal diseases remain the most prominent, prevalent and costly oral health problems worldwide.

The 1987 NIDR survey of U.S. school children aged 5-17 showed a dramatic decrease in tooth decay with approximately one-half of the children being caries-free in their permanent teeth. However, 84 percent of all 17-year-olds surveyed had experienced tooth decay in their permanent teeth. Recent analysis of the survey findings indicate that children who always had been exposed to community water fluoridation had caries scores significantly lower than did those who had never lived in fluoridated communities. The results indicate that water fluoridation plays an important role in the decline of caries and must continue to be a major prevention methodology.

Fluoride in toothpastes, mouthrinses, topical gels, prescription tablets, and food processed with fluoridated water is commonplace today. Mild tooth fluorosis has been observed in some children on clinical examination. Epidemiological studies are being carried out to determine the prevalence of dental fluorosis. Scientists are testing fluoride in combination with other substances or vehicles in mouthrinses that increase the effectiveness of lower levels of fluoride in preventing tooth decay. Fluoride studies in animals are assessing its bioavailability, incorporation into hard tissues, and the effect of its interaction with minerals and other dietary components on its absorption and assimilation.

Adult oral health fails to demonstrate a decline in dental decay prevalence similar to the one seen in children. Although adults experience coronal caries, the major type in children, they also have caries on the exposed roots of teeth (root surface caries). Epidemiologists are conducting studies to determine the prevalence and incidence of root caries and coronal caries in elderly and compromised groups. They have identified associations between root caries and a variety of clinical, laboratory, dietary, and psychosocial correlates. One study found that people who lived in non-fluoridated areas for 30 years or more had a greater risk of both coronal and root caries.

The most recent adult survey (NIDR, 1985-86) also found that nearly 80 percent of all employed adults have some form of periodontal disease, and both prevalence and severity of these diseases increases with age. In this population, untreated dental decay, gingivitis, and more advanced periodontal diseases can be painful, interfere with chewing ability and speech, alter the choice and taste of foods, and affect general health. Clinical studies of periodontal diseases in older adults are characterizing the factors which discriminate among older Americans with and without periodontal destruction. One aspect of the studies is to collect food intake data in order to estimate percentage RDA for important nutrients and to determine if a relationship can be established between diet and/or nutrition and disease.

Although dental caries among children and younger adults, as well as some forms of adult periodontal disease, appears to be declining, the overall prevalence of these conditions still imposes a substantial burden on Americans. The NIDR is now expanding its programs and efforts to include the oral health concerns of adults and older Americans--the segments of the population that are continuing to grow so rapidly. The NIDR also emphasizes the need to identify for early prevention individuals at high risk for oral diseases and the need to improve or modify research methods and measurements to document the knowledge, attitudes, and behaviors of low-income, nutritionally deprived, low-education persons, and other groups at high risk for disease.

The NIDR has begun a major initiative called the "Research and Action Program for Improving the Oral Health of Adults and Older Americans." The genesis for this program lay in findings from the 1985-86 NIDR National Survey of Oral Health of United States Adults. The survey established that there have been substantial gains in oral health among employed adults, and even among our oldest citizens, compared to a generation ago. Nevertheless, over 40 percent of men and women 65 years old or older are missing all their teeth. Those who still have teeth continue to experience tooth decay and suffer more severe and extensive gum diseases than do younger adults.

The NIDR initiative is designed to spur the basic and clinical research necessary to drive nationwide public and private sector actions to improve the oral health of all Americans. The explicit goal of the program is to eliminate tooth loss in the U.S. population and prevent further deterioration of the oral health status of individuals who have a compromised dentition. The NIDR role will be to expand the knowledge base and accelerate the transfer of laboratory findings to the public and to the profession. The Institute is emphasizing research on normal changes in the oral tissues and the body's defense mechanisms in aging, and how these changes are affected by disease, diet, medications, environment, and lifestyle. Epidemiologic and behavioral science research will be essential to document the prevalence of oral diseases in special populations (e.g., the frail; the handicapped), identify risk factors, advance prevention research, and monitor science transfer.

Two other ongoing studies of interest involve malnutrition and tooth development, and passive immunization with antibodies in bovine milk. Extramural scientists have shown that rats can be protected against dental caries by passive immunization with milk antibodies, obtained from hyperimmunized cows, to dental caries-causing bacteria. In a preliminary study, they also have observed that human volunteers using, as a daily mouthrinse, bovine immune whey which contained the antibodies to the caries-causing bacteria, showed a decrease in the number of bacterial cells in dental plaque as compared with subjects rinsing with a control whey without the antibodies.

Other dental investigators in international collaboration with dentists in Peru are carrying out a longitudinal study designed to evaluate the effect of early malnutrition on oral tissue development and susceptibility to dental caries in the deciduous teeth. Dental evaluations conducted in children at 12, 18, 24 and 30 months of age revealed that children who have suffered both chronic and acute malnutrition during their first year of life show a delayed eruption of their teeth and have a rate of caries attack that is seven times greater than that of normal children.

The NIDR also focuses on the relationship of human diet both to the incidence of dental diseases, especially dental caries, and to the caries-inducing and caries-inhibiting potential of various foods. Efforts are under way to identify naturally occurring and synthetic noncariogenic sweeteners (potential substitutes for table sugar) and food constituents that have cariostatic properties. The effects of such substances on supragingival dental plaque formation and on the cariogenic potential of oral bacteria are being studied.

Nutritional Deficits and Oral Disease

Multiple nutrient deficiencies have been shown to increase the permeability of oral epithelia in experimental animals. As a result, the animals' tissues appear to become more vulnerable to periodontal diseases and soft tissue lesions, conditions analogous to those seen in human nutritional deficiencies.

Decreased salivary flow rate, directly or indirectly related to dietary intake, has been shown by NIDR-supported scientists to result in predictable patterns of increased dental caries and gum inflammation. Subclinical nutritional deficiencies of vitamin C and folic acid have been found to worsen periodontal problems, both in humans and in nonhuman primates. Other deficits, including lack of iron, folate, and vitamin B_{12}, have been linked to the development of aphthous inflammation of the oral mucous membranes.

RESEARCH DIRECTIONS

NIDR's nutritional research focuses on the relationship between diet and the development and maintenance of both hard and soft tissues of the oral-facial complex. Special interests are in the problems of tooth and gum development and maintenance, periodontal diseases, and dental caries, particularly as they are affected by nutritional factors. Examples of nutrition research supported by the NIDR are as follows:

- Basic studies on the systematic effects of nutrients during embryonic life, particularly as they relate to oral structures, e.g., the role of nutrition in craniofacial malformations and developmental defects of cleft lip and palate.
- Investigations to determine the effects of poor nutrition on the fundamental integrity and metabolism of healthy oral mucous membranes, e.g., the effect of nutrition on salivary gland function, including the secretory immune mechanism.
- Research on the effects of nutrition on the biology of bone and soft tissue, the etiology and prevention of oral ulcerative diseases, and immunization against oral infections.
- Research to define the critical periods of development of dental tissues that may be sensitive to nutrient intake and the role of nutritional factors in the maintenance and repair of the periodontium and oral tissues.
- Research on the role of nutrition and nutritional status in the etiology and pathogenesis of dental diseases in older persons and other high-risk populations.
- Examination of the metabolic effects of various fluoride levels in humans, especially the effect of fluoride received prenatally, and investigation of dental fluorosis.
- Studies on the effects of zinc deficiency in pathologic stimulation of activity of epithelium lining in some regions of the oral cavity.
- Investigation into the structure, nutritional requirements, and normal functioning of salivary components such as mucins (important in lubrication), histidine-rich proteins (with specific antifungal properties), and proline-rich proteins (important in remineralization of tooth enamel). Scientists also are studying salivary gland dysfunction, particularly as a result of cancer therapy.
- Research on the effect of dietary factors, such as vitamin A, vitamin E, and alcohol, on the initiation and progression of oral cancers.

OUTLOOK

Complementing its continuing interest in the role of nutrition and diet in the oral health of children and young adults, the NIDR will increase research efforts directed toward the growing aged population. Dietary and nutritional studies of older individuals will be conducted to determine how food choices and the overall nutritional status of this population affect oral health and influence general health status. Defining the relationship between appropriate nutrition and oral health from the prenatal period throughout the life span is an important concern of the NIDR.

For more information on the NIDR nutrition program, contact:

Joseph E. Ciardi, Ph.D.
Caries and Restorative Materials Research Branch, Extramural Program
National Institute of Dental Research
Westwood Building, Room 504
National Institutes of Health
Bethesda, MD 20892
(301) 496-7884

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

Since its creation in 1950, the NIDDK's research responsibilities have included nutrition-related programs to prevent and treat disorders such as liver and biliary diseases; pancreatic diseases; gastrointestinal, digestion, and absorption disorders; diabetes; obesity; a variety of endocrine disorders; kidney and urological diseases; metabolic diseases, including cystic fibrosis; and eating disorders. The NIDDK plays an important role in the study of nutritional factors relating to the etiology, prevention, and treatment of diabetes, digestive, and kidney diseases. This research is supported out of three divisions: the Division of Diabetes, Endocrinology, and Metabolic Diseases; the Division of Digestive Diseases and Nutrition; and the Division of Kidney, Urologic, and Hematologic Diseases.

PROGRAM HIGHLIGHTS

Omega-3 Fatty Acids

The role of omega-3 fatty acids in human health is being actively investigated. Recent epidemiologic, clinical, and experimental data suggest that omega-3 fatty acids, which are highly polyunsaturated fatty acids derived from linolenic acid, may have important physiologic effects that cannot be met by omega-6 or omega-9 fatty acids. Linolenic acid, the most common dietary polyunsaturated fatty acid, is the precursor of prostaglandins that regulate platelet aggregation and, accordingly, the processes associated with blood clot formation. Institute-supported investigators have studied the effects of omega-3 fatty acid feeding on the metabolism of lipoproteins in normal persons and those with genetic forms of hyperlipidemia--higher than normal cholesterol and lipoprotein levels in the blood. Their findings showed decreased low density lipoprotein cholesterol and apoprotein B, a protein component of lipoproteins, in normal persons and in those with familial hypercholesterolemia--an inherited disorder characterized by a high level of serum cholesterol and early development of atherosclerosis. However, in familial combined hyperlipidemia, the levels did not improve and even worsened in some patients.

Institute scientists also studied the relationship of omega-3 fatty acid feeding to the problem of insulin insensitivity in diabetes mellitus. They found that with 8 grams of omega-3 fatty acid supplementation daily over an 8-week period, fasting glucose levels rose by 22 percent and meal-stimulated glucose increased by 35 percent. Plasma triglycerides and low density lipoprotein levels fell during the omega-3 fatty acid supplementation period. Although omega-3 fatty acid supplementation did improve plasma lipoprotein levels, it resulted in a deterioration of glucose homeostatis in diabetics not on insulin or on oral drugs.

Despite researcher's lack of a clear understanding of omega-3 fatty acids value to humans, recent work in nonhuman primates indicates that they are essential to the normal development and functioning of the retina and brain. At present, changes in retinal function provide the best evidence for the functional effects of omega-3 fatty acid deficiency in mammals. One compound, called docosahexaenoic acid, is the major polyunsaturated fatty acid in the photo receptor membrane of the retina and in cerebral gray matter.

Cytokines

Tissue injury is thought to result in the generation of a hormone-like protein that causes significant effects on a person's immunologic and metabolic functions. That protein is an intercellular mediator cytokine called tumor necrosis factor or cachectin. Persistent cachectin production takes place during chronic infection and maligancy. This results in a cachexia syndrome, characterized by anorexia, weight loss, and anemia. Cachectin is capable of causing lethal shock. Scientists have shown that when they inhibit cachectin with monoclonal anticachectin antibodies during a case of overwhelming gram-negative bacteria in the blood, it confers protection against septic shock. Although unprotected controls died within hours, baboons immunized against cachectin did not develop the characteristic increases of serum counter-regulatory stress hormones and did not die, suggesting that cachectin is a critical mediator of the deleterious responses to bodily infection.

Recent research with supplementary omega-3 fatty acids in nine healthy subjects showed that the volunteer's peripheral blood cells did not readily synthesize tumor necrosis factor, or cachectin. Dietary supplement with omega-3 fatty acids resulted in a 50 to 70 percent reduction in the synthesis of cachectin, which may help to explain the ameliorative effects of omega-3 fatty acid diets on certain diseases.

Obesity

According to estimates, 26 percent of the U.S. adult population is overweight--about 34 million people age 20 to 75. When weight changes, adipose sites increase or decrease in size. This results from the decomposition of fat, lipolysis, which releases fatty acids, and reesterification, which controls the storage of fatty acids such as triglycerides within the cell. Lipolysis is at least in part under the control of adrenergic receptors, which are the protein molecules recognizing chemical substances that stimulate the sympathetic nervous system. The several types of adrenergic receptors are demonstrated by the effects of several chemical substances (catecholamines) on the receptors. Two specific types, beta_1 and alpha_2 receptors, predominate in the plasma membranes of human fat cells. These two receptors have opposing effects on lipolysis: beta_1 stimulates, and alpha_2 inhibits. Response to norepinephrine (which activates both receptors) is greater in the abdominal tissue of the female than is in the male. Given the apparently equal degrees of beta responsiveness in the abdominal tissue of males and females, the data for norepinephrine suggest that males have more abdominal alpha_2 receptor function than females. This difference may partially explain the greater tendency for male subjects to accumulate adipose tissue in the abdominal region. At equal amounts of abnormal weight, the risk of associated problems such as hypertension, stroke, ischemic heart disease, and Type II diabetes is greater in individuals with predominately abdominal as opposed to gluteal fat deposits (high waist:hip circumference ratio).

In other research, Institute-supported scientists conducting research on diabetes, overweight, and risk factors for obesity among the Pima Indians of Arizona have demonstrated that the resting metabolic rate, which is unique to each individual, is a familial trait. Using a metabolic chamber equipped as living space, the investigators measured the resting metabolic rate and 24-hour energy expenditure over a 2-year period. They found individuals with the lowest resting metabolic rates gained the most weight over a subsequent period of observation. The resting metabolic rate was found to predict the observed gain in body weight over a 4-year follow-up period. A low rate of energy expenditure may contribute to the occurrence of obesity in families because an inherited lower energy requirement makes it that much easier to consume more food than the individual's energy requirement calls for. This study clarifies that people with an inherited "slow" metabolism are at higher risk for becoming obese than are people with normal or higher-than-normal metabolic rates. Consequently, individuals with a familial low resting metabolic rate need to be even more careful about restricting their calorie intake.

To examine the relationship of body composition to energy expenditure, NIDDK-supported researchers measured energy expenditure in two groups of men who were matched with respect to body weight, and who had the same degree of overweight. One group was obese and the other overly muscular and lean. The fasting resting metabolic rate was significantly greater for the lean as opposed to the obese men, except when expressed relative to lean body mass. Also, the thermic effect of food was greater for the lean men. The investigators found that the obese men had reduced energy expenditure and a diminished capacity for thermogenesis. Next, to clarify the relationship between obesity and thermogenesis, the researchers investigated matched lean and obese male groups who differed in body fat content. Although resting metabolic rate was not significantly different for the lean men, the thermic effect of food was "blunted" in the obese men, supporting the idea that body fatness rather than absolute quantity of lean tissue is the major determinant of the thermic effect of food. Consequently, obesity is associated with diminished thermogenesis.

Other studies investigated three age-matched groups of men to relate obesity and overweight to cardiovascular risk factors and sex steroid levels. The groups were: normal weight; overweight, obese; and overweight, lean. Estradiol was 25 percent greater in the overweight lean group. Total testosterone was significantly lower in the obese. Neither level was correlated with lipid levels. The cardiovascular risk factors were not significantly different between the normal and overweight lean groups. However, body fat was significantly correlated with systolic blood pressure, plasma insulin, low density lipoprotein levels, and high density lipoprotein/total cholesterol levels. The researchers found that individual body composition parameters (percent body fat and total body fat mass) were significantly related to cardiovascular risk factors.

Nutritional Management of Premature Infants

Almost all infants weighing less than 1,200 gm require intravenous feeding, or total parenteral nutrition (TPN), for the first weeks of life. Researchers are trying to determine the blood and urine concentrations of nutrients in these very low birth weight infants. Because of renal and possibly hepatic immaturity, the presently recommended doses of riboflavin (vitamin B_2) are too high and can produce blood levels of this vitamin in excess of 100 times that normally present. Also, in the same group of infants, there is a 4- to 6-fold elevation of plasma B_6 vitaminers. In addition, a chronic lung disease called bronchopulmonary dysplasia, which occurs in these infants due to an inability for their lungs to heal following respiratory support, has been linked to vitamin A deficiency. The researchers have shown that 50 percent of these very low birth weight babies have vitamin A deficiency despite supplementation; the problem can persist up to one month after the infants are on oral feedings. The investigators have demonstarted that 85 percent of vitamin A added to TPN is lost in the intravenous delivery system, and that the losses and the deficiency can be prevented by the addition of vitamin A to an intravenous lipid emulsion.

RESEARCH DIRECTIONS

The NIDDK fosters and supports other nutrition research and training, especially in the following broad areas of fundamental and clinical nutrition:

- Research on dietary requirements (and safe levels) of many nutrients needed for health maintenance, proper growth and development, and a state of well-being at all ages and under various conditions such as stress, drug use, nutrient imbalances, and changing activity levels.
- Fundamental studies exploring nutritional factors that are active in absorption and metabolism, the biological control of such processes, and the identification of unrecognized roles of nutrients or their metabolites.
- Studies on the detrimental effects of iron deficiency in terms of such factors as work capacity and performance, physical and mental development and function, susceptibility to infection, and perinatal morbidity and mortality.
- Assessment of the impact of omega-3 fatty acids on prostaglandin biosynthesis and metabolism, their influence on membrane function, and their potential role in the development and progression of disease processes.
- Research on fiber to determine its chemical characteristics in order to determine its effects on intestinal microflora and food transit time; its interaction with nutrients, bile acids, and other substances in the gut; its effects on digestive enzymes and absorption; and the development of improved routine methods for analyzing its components.
- Assessment of the requirement levels and metabolic roles of trace elements, with the help of reliable, newly developed, analytical methods.
- Research on relationships between genetic predisposition, induced metabolic changes, thermogenesis, environmental and physiological factors, and lifestyles that result in greater energy intake than expenditure (for obesity prevention and control).
- Development of methods for characterization of various types of obesity and determination of the health consequences of repeated cycles of weight gain and loss.
- Investigation of how chronic feeding of diets high in fat and glucose increases blood pressure and enhances sympathetic nervous system activity in rats.
- Studies to determine how widely used body weight depressants work in rats.
- Research on the diverse alterations in carbohydrate metabolism seen during injury or infection in rats.

- Investigations on how dietary polyunsaturated fats uniquely regulate fatty acid synthetase in rats.
- Determination of the most effective individual, group, and community intervention strategies for weight management.
- Investigation into the contribution of genetic and metabolic factors to obesity causation, including the molecular and genetic basis of energy metabolism and the nature of genetic aberrations in human obesity.
- Research to improve nutritional support to hospitalized patients, to improve nutritional status assessment methodology, and to acquire more information about the effects of disease states on the nutritional needs of patients.
- Investigation of dietary modifications that may retard the rate of progression of end-stage renal disease, reduce the need for dialysis, or both.
- Research to determine the relationship of the role of dietary protein to that of phosphate in protein's effect on kidney function.
- Investigation of the mechanisms by which other nutrients such as fatty acids or amino acids might affect renal function.
- Studies of the causes of wasting, malnutrition, and other nutritional disorders that occur in renal failure.
- Research on the interplay of dietary factors (such as calcium, vitamin D, phosphate, protein, and oxalate) in the etiology of renal stones.
- Studies on the role of calorie intake and physical activity, and subsequent weight control, in the prevention of Type II diabetes.
- Investigation of the metabolic mechanisms of intestinal and hepatic processing of dietary carbohydrate, and the effects of other nutrients and of fiber on carbohydrate metabolism.
- Clinical research into nutrition-related areas such as cholesterol and pigment gallstones; inborn errors in bile acid metabolism; chronic hepatitis that evolves from autoimmune, viral, or alcoholic disease; and various liver diseases such as Wilson's disease and portal hypertension.
- Investigations into the control of appetite, satiety, and anorexia in normal individuals as well as in those with various disease states.
- Exploration of mechanisms for the development of gastrointestinal malabsorption in AIDS patients and investigations of other metabolic perturbations of nutrient metabolism among AIDS patients such as lipogenesis to develop rational means of nutritional support of these patients.
- Funding of five Clinical Nutrition Research Units and the Obesity Core Center, each conducting an intensive program of nutrition research.

OUTLOOK

The NIDDK's investigations into nutritional requirements in health and disease and into the role of diet in disease prevention and health promotion ultimately will affect national health and productivity.

Working in conjunction with other NIH institutes, the NIDDK shares responsibility for advancing fundamental knowledge of the processes and programmatic changes that will lead to needed alterations in American dietary habits.

For more information on the NIDDK nutrition program, contact:

Van S. Hubbard, M.D., Ph.D.
Director
Nutritional Sciences Branch
National Institute of Diabetes and Digestive and Kidney Diseases
Westwood Building, Room 3A18B
National Institutes of Health
Bethesda, MD 20892
(301) 496-7823

NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE

Stroke ranks third as a cause of death and occurs in about 500,000 persons per year in the U.S., resulting in nearly 150,000 deaths in 1987 and long-term disability for many individuals. Other neurologic conditions are also prevalent in the U.S. population. For example, approximately 2 million Americans suffer from epilepsy, chronic headaches afflict 40 million people, and Alzheimer's disease affects 2 to 3 million citizens.

Since its creation in 1950, the mission of the NINCDS has been directed toward finding the cause of, preventing, diagnosing, and treating neurological disorders and stroke. This mission is accomplished through the NINCDS Division of Communicative and Neurosensory Disorders; the Division of Fundamental Neuroscience; the Division of Convulsive, Developmental, and Neuromuscular Disorders; the Division of Demyelinating, the Atrophic, and Dementing Disorders; the Division of Stroke and Trauma; and the Division of Intramural Research.

PROGRAM HIGHLIGHTS

Knowledge of the extent of interaction among diet, nutrition, and the nervous system in humans is evolving, rapidly changing, and as yet controversial and inconclusive. The nervous system (central and peripheral; somatic and autonomic) is influenced, in its state of normalcy and of disease, by intake of carbohydrates, fats, proteins, minerals, vitamins, and trace elements. The precursors of neurotransmitters, which transmit messages between neurons and supporting cells in the nervous system, are predominantly amino acids. More research is needed to elucidate the interaction between quality and quantity of food intake and its effect on neurologic functions such as appetite, hunger, sleep, brain development, memory, and cognition. Also requiring continued research effort is the possible role of nutrition in neurological disorders (e.g., stroke, headache, epilepsy, certain vitamin deficiency and toxicity syndromes, Alzheimer's disease, Parkinson's disease (PD), tardive dyskinesia, Huntington's disease, Gilles de la Tourette's syndrome, birth defects, Wilson's disease, hemochromatosis, and amyotrophic lateral sclerosis (ALS). Similarly, studies are under way to investigate toxins (food-borne and endogenous), food additives (such as aspartame), and drug-nutrient interactions to elucidate their mechanisms, if any, on nutrition and the nervous system.

The brain and nervous systems appear to require a full complement of essential nutrients and energy to develop and maintain their neurons and supporting cells.

The Role of Diet in Cerebrovascular Disease (Stroke)

Stroke is the sudden loss of brain function caused by one of four vascular events: thrombosis, or blood clot, in a cerebral artery; embolism, or blockage, of a cerebral artery by a circulating clot; stenosis, or narrowing, of a cerebral artery by atherosclerosis; or hemorrhage from rupture of a cerebral artery. Symptoms range from those too trivial for the person to notice to major sensory deficits, blindness, paralysis, speech loss, coma, and death.

The effects of specific dietary factors on the causation of stroke warrant investigation. The longitudinal population studies of Framingham, Olmsted County, and Copiah County have collected data on a variety of factors, including diet, that may be considered risk factors for stroke. Epidemiologic evidence associates excessive alcohol consumption with increased frequency of subarachnoid hemorrhage and cerebral infarction, and heavy alcohol intake may be an independent risk factor for stroke in humans.

Studies are under way in man to evaluate the effects of certain diuretics (thiazides and amilorides) on salt consumption, salt taste sensitivity, and salivary flow composition, to aid in the development of optimal therapeutic practices for patients requiring such treatment.

Hypertension is a major risk factor for stroke. Evidence links dietary factors to high blood pressure, diabetes, and obesity and supports the relationship between dietary fat, blood cholesterol, and atherosclerosis, especially of the coronary arteries. However, a similar association to intracranial cerebral arteries and stroke is not yet finally established.

Nutrition and Neurologic Disorders

A high incidence of neurologic disorders such as kuru, ALS/PD, epilepsy, spastic paraparesis, familial parkinsonism, as well as schizophrenia, neoplasms, goiter, cretinism, diabetes, asthma, malaria, filariasis, and cysticercosis has been reported to occur more frequently in certain geographic locations worldwide. NINCDS intramural scientists study nutrition, reproduction, polymorphisms, genetic distance, and so forth in natural cultural experiments in areas of high incidence of such diseases in Micronesia, Polynesia, Solomon Islands, New Hebrides, New Guinea, Indonesia, South America, Asia, and Africa. Intramural scientists in these regions have been studying a long-standing hypothesis about the high incidence of ALS and PD. One study showed that the soils from southern Guam had a 10- to 100-fold lower mean calcium concentration when compared to mean concentrations for the central and northern regions of the island. The concentration of calcium in the drinking water was geographically parallel to calcium levels in the soil; the mean calcium concentration in drinking water from southern Guam was approximately three times less than that from central and northern Guam. Approximately 30 percent of the Chammorros (native people of Guam) with ALS and PD had biochemical evidence of disturbances in calcium and vitamin D metabolism, and the Guamanian children and adults have cortical bone loss. Intramural scientists are able to determine qualitatively and semiquantitatively both the intracellular and extracellular distribution of minerals and trace elements within the central nervous system (CNS). Methods have clearly demonstrated the prominent accumulation of calcium, aluminum, and silicon in neurofibullary tangle (NFT)-bearing neurons in the brain and spinal cord of ALS and PD patients. The elemental images clearly show the striking colocalization of these elements within the cell body and dendritic processes of the same NFT-bearing neuron. The semiquantitative estimates of the calcium, aluminum, and silicon concentrations (weight fraction) in the NFT-bearing neurons from ALS and PD patients were 7,200, 500, and 3,000 ppm, respectively. However, dietary intake of these nutrients has not been shown to be causal and investigations are under way to determine the mechanism to explain this deposition of calcium, aluminum, and silicon concentrations in these individuals with ALS and PD as well as the similar brain depositions measured in Alzheimer's patients in the U.S. Despite the rapid disappearance of ALS and PD from Guam, the role of dietary patterns in the etiology of these diseases is still controversial and of experimental interest.

Studies are being conducted in rats to explore the relationship between dietary protein deficiency and increase in dopamine in the neostriatum, with respect to age, duration of effect, and mechanism interaction. These include which chemically discrete neurons mediate the effect of food intake, and what ingestive changes are observed after damage to certain parts such as the area postrema solitary nucleus.

Experimental studies under way in animals seek to understand the role of the hindbrain in the control of appetite. Investigations are concerned with which chemically discrete neurons mediate the effect of food intake, and what ingestive changes are observed after damage to certain parts such as the area postrema and solitary nucleus.

Studies involving local injections and brain lesioning are conducted in rats in order to investigate the role and mechanism by which the newly discovered brain peptide, neuropeptide Y (NPY), stimulates appetite (orexigenic) and the pathogenesis of anorexia of aging. Drinking accompanying NPY-induced eating, and the relation of NPY to norepinephrine-induced eating, and NPY tolerance development are being studied.

Studies on the effects of aspartame on the central nervous system are being conducted to understand the underlying mechanism of interaction between this increasingly used artificial sweetener and the brain level of phenylalanine and tyrosine, with and without the concomitant ingestion of a carbohydrate meal. Other aspects of this study are the effect of blood pressure and the release of catecholamines from physiologically active neurons, and the impact of aspartame dose on food intake and nutrient choice.

RESEARCH DIRECTIONS

Among a host of other NINCDS-supported research efforts, the following appear to offer promise of uncovering links between nutrition and neurologic functioning:

General

- The nutritional needs of the brain and nervous system in health and throughout life.
- The understanding of the blood-brain barrier nutrient transport processes and of the mechanisms by which diet may influence brain function and health.
- The relationship, if any, between specific dietary factors and specific brain functions such as memory, alertness, and response time.
- The mechanisms by which food components such as dietary precursors of neurotransmitters and certain additives and toxins might affect nervous system function.
- The effects of excessive intake of nutrients and supplements (e.g., vitamin A or vitamin B_6) on nervous system function.
- The role of specific dietary factors in the etiology and prevention of neurologic disorders such as stroke, Alzheimer's disease, and Parkinson's disease.
- The most effective methods to educate the public: (a) about the relation between diet and the normal functioning of the nervous system, (b) about diet-related risk factors for neurological diseases and, (c) to assist the public in making recommended dietary changes.
- The role of preexisting nutritional disease and nutritional status on the impact of neurotoxins.

Specific

- Studies evaluating the effects of certain diuretics (thiazides and amilorides) on human salt consumption, salt taste sensitivity, and salivary flow composition. Findings may improve the therapeutic outlook for patients requiring such treatment.
- Studies conducted in rats to explore the relationship between protein deficiency and an increase in the neurotransmitter dopamine in the neostriatum. The investigations may yield important information on such matters as the interaction between uptake of dietary tyrosine and the brain's production of dopamine. This could help physicians devise more effective therapy for patients with Parkinson's disease, which has the characteristic reduction of dopamine in the neostriatum.
- Experimental studies conducted in animals to define the role of the hindbrain in the control of appetite. The NINCDS-funded scientists are attempting to discover which chemically isolated neurons mediate the effect of food intake, and what ingestive changes are observed after damage to certain regions of the hindbrain.
- Studies conducted in rats to explore the means by which the newly discovered brain peptide neuropeptide Y (NPY) stimulates appetite. Conversely, the pathogenic loss of appetite among the aging may also be clarified. Investigators will study drinking accompanying NPY-induced eating, the relationship of NPY to norepinephrine-induced eating, and NPY tolerance development.
- Studies on the effect of aspartame on the central nervous system.

For more information on the NINCDS nutrition program, contact:

Zekin Shakhashiri, M.D., M.Sc., M.P.H.
Senior Medical Officer
National Institute of Neurological Disorders and Stroke*
Building 31, Room 8A05
National Institutes of Health
Bethesda, MD 20892
(301) 496-9271

**In FY 1989, the National Institute on Deafness and Other Communication Disorders (NIDCD) was created by an act of Congress and the name of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) was changed to the National Institute of Neurological Disorders and Stroke (NINDS).*

Interactions among nutrition, infections, immune disorders, and allergies have important implications for the health of the American population and around the world. Asthma and allergic diseases affect over 40 million Americans. In 1980, in the developing world, where food and water supplies are often contaminated with microorganisms, more than 1 billion cases of diarrheal diseases were estimated to occur in children under the age of five. Despite high standards of sanitation in the U.S., the incidence and costs of food-associated disease are considerable.

The NIAID was established in 1948, although the 1887 Laboratory of Hygiene, a bacteriological laboratory, was the forerunner of the Institute.

PROGRAM HIGHLIGHTS

NIAID's nutrition studies are an integral part of Institute research to lessen the adverse health consequences of allergic and infectious diseases. Institute studies are examining the modulating effects of specific nutrients (e.g., amino acids, vitamins, minerals, trace elements, and fatty acids) on basic immune functions. Of particular significance may be the effects of iron, zinc, and related elements on microbial virulence.

Food-borne microbial illness and the prevalence of infections among malnourished persons are of continuing research interest. NIAID is also investigating whether food allergy may play an important role in gastrointestinal disease.

Other continuing concerns are the effect of malnutrition on resistance to infections, especially infectious diarrhea in children; the role of breast milk as a defense against enteric infections; and the effect of infections on nutritional status.

Nutrition and AIDS

Since recognition of acquired immunodeficiency syndrome (AIDS) in 1981, the NIAID has conducted a full-scale program of basic and clinical research against this disease, now recognized as a national health emergency.

Infection by the immunologically devastating human immunodeficiency virus (HIV) sets the stage for weight loss and deteriorating nutritional status in the AIDS disease process. Common features of advanced AIDS are loss of appetite, nausea, vomiting, diarrhea, and malabsorption of fats, carbohydrates, and protein.

The NIAID mission in developing and testing potentially useful drugs against AIDS presupposes the maintenance of AIDS patients in optimal health. Studies have indicated, for instance, that protein malnutrition, coupled with certain forms of drug therapy, decreases the immunologic defense system and predisposes to *Pneumocystis carinii* pneumonia, the leading cause of death among AIDS patients. These studies are discussed in more detail in section 3.

Trace Elements and Immune Function

Severe malnutrition due to any cause will impair the body's normal cell-mediated immunity and may diminish the immunity effected by antibodies circulating in the blood and secreted by mucosa.

Lack of appropriate amounts of trace elements in the diet may contribute to severe immunologic deficits. Deficits of trace metals such as iron and zinc are already known to impair neutrophil function.

NIAID investigators are probing the effects of abnormally low levels of protein and zinc (individually and in combination) on the efficacy of the antituberculosis vaccine BCG. They are exploring the influence of endotoxins on the way the body is able to utilize zinc and copper, and they are examining the synergistic host defense role of fever as affected by changes in plasma iron and copper levels.

Food Allergy

The Institute's research program on allergic disease factors includes a broad spectrum of studies. Food allergy may play an important role in gastrointestinal disease, but little is known of how widespread the problem is, nor of its mechanism of action or effect on gastrointestinal function. Recently, an NIAID-sponsored Food Allergy Working Group was established to develop clinical definitions, standardize the composition of designated food allergens, and conduct clinical studies of food allergens using standard protocols. Investigators are also working to develop standard diagnostic tests to determine who may be at risk from allergic reactions to foods.

Other NIAID-funded research has shown that food allergy is a cause for skin symptomatology in up to one-half of a selected group of children with severe atopic dermatitis. Increasing recognition of the role of food allergies in disease should lead to improved diagnosis and patient care and to a corresponding decrease in medical expenses.

RESEARCH DIRECTIONS

The NIAID's interest in nutrition lies in advancing knowledge of the complex interrelationships of nutrition with immunity and infection. The Institute's research directions are correspondingly varied. They include:

- Investigations on the relationship of food allergies and the immune response to ingested antigens and orally induced immunological response to proteins.
- Research on the role of minerals, especially iron, on the metabolism and virulence of fungi and bacteria, and studies on nutritional immune response to worms and one-celled parasites and factors that may alter human related diseases, including schistosomiasis, giardiasis, and cryptosporidiosis.
- Investigations of the modulating effects of specific nutrients (e.g., vitamins, trace elements, amino acids, and fatty acids) on basic immune functions.
- Studies on the negative effect that malnutrition has on resistance to tropical infections (especially infectious diarrheas), the role of breast milk as a defense against enteric infections, and the usefulness of improved oral rehydration salts in the management of dehydration and diarrhea.
- Research into the interaction between nutrition and infection in American hospitals, as part of a program on hospital-associated infections. Included are epidemiological studies of hospital-acquired infections and malnutrition in different clinical situations; studies on the effects of hypercatabolic illness on immune function and resistance to infections; studies on the effect of enteral and parenteral nutritional support on immune function and hospital infections; and studies on nutrition and intestinal dysfunction in AIDS.

OUTLOOK

In the past decade, significant advances have been made in knowledge of the interactions among nutrition, infections, and immune disorders, yet much remains to be learned of this complex three-way interrelationship. Intensified research on infectious diseases such as AIDS may provide scientific advances that help to clarify these important, unresolved questions. Thus NIAID programs are designed to improve nutritional status, offering patients and the research efforts in which they participate the greatest opportunity for successful outcome.

For more information on the NIAID nutrition program, contact:

Daniel I. Mullally, M.D., M.P.H.
Division of Allergy, Immunology, and Transplantation
National Institute of Allergy and Infectious Diseases
Westwood Building, Room 754
National Institutes of Health
Bethesda, MD 20892
(301) 496-7353

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

The mission of the Institute is to support basic, undifferentiated biomedical research and research training, which undergird all biomedical investigations. Established as a division in 1958 and as an institute in 1962, the major focus of the NIGMS is on research concerned with expanding knowledge of fundamental biological structure and function at the cellular and molecular level. Studies include investigations in the biophysical and physiological sciences, the structure and function of the cell, the basic mechanisms of heredity, and the molecular aspects of the interactions between therapeutic drugs and their target tissues or organs.

PROGRAM HIGHLIGHTS

Most of the nutrition-related research is supported by the NIGMS in its trauma and burn program area, focusing on the underlying mechanisms of the body's systemic responses to trauma, including burn injury. Accordingly, research on the nutritional requirements of convalescing patients is of key interest to the Institute. Since an understanding of the role of nutritional status is essential to many ongoing clinical investigations, the answers to several research questions may be found in these studies. The rational practice of nutritional support in trauma patients comes from an understanding of the metabolic response to injury and its effects on intermediary metabolism. In this connection, NIGMS-supported scientists are exploring nutritional requirements following severe trauma and sepsis, new concepts in parenteral therapy, branched chain amino acid feeding during injury, and cellular response during shock.

Nutrition and the Trauma Patient

Recent highlights in the area of nutritional requirements and therapy in the traumatized patient have focused on the metabolic response to trauma and its association with a crisis of energy availability.

Generally, the metabolic response to severe trauma includes enhanced energy expenditure, hyperglycemia with increased glucose tolerance, insulin resistance, enhanced muscle wasting with accelerated protein kinetics, and persistent fat fuel utilization. Associated with these dynamic changes in metabolism is an altered hormonal environment. NIGMS-supported researchers have been investigating the mechanisms that generate these metabolic responses.

Preservation of body proteins is an important goal in the post-traumatic period; loss of body protein results in functional muscle impairment. Investigators supported by the NIGMS are studying the increased loss of body nitrogen following injury and have demonstrated that there is a significant correlation with the magnitude of injury and body nitrogen levels. Starvation and inactivity occurring at various stages of injury exacerbate the metabolic response.

Following major injury, enteral and parenteral feeding have been found to improve the patient's negative nitrogen balance. In addition, the administration of branched chain amino acids and pharmacological doses of insulin and growth hormone have been shown to improve nitrogen economy. Studies are also under way to explore the impact of the route of nutritional support on the hypermetabolic response to burn injury during the initial resuscitation and later nutritional support phases.

NIGMS-supported investigators are also studying the molecular mechanisms of altered glucose metabolism and are investigating the effects of providing calories in the form of carbohydrates and amino acid supplements as nutrients in order to meet the extra metabolic needs of burn and trauma victims. Studies are also being conducted on the mechanisms for the increase in the use of body fat as a major fuel source in response to trauma and septic shock. Results of these studies have provided evidence that stimulation of the beta receptors following trauma results in increased free fatty acid mobilization.

Research in the nutritional needs of the whole animal in association with tissue repair is another area supported at the NIGMS. There is an increased requirement for vitamin A following injury. Studies have shown that vitamin A, when given as a dietary supplement, promotes the healing of wounds as a result of its ability to enhance fibroplasia (the forming of fibrous tissue), and collagen accumulation.

In addition, new studies seek to identify repletional factors such as polyamines, which contain two or more amine groups and can be used as markers. Such factors insure the timely effectiveness of nutritional support prescribed by the physician and improve the clinical management of a critically injured patient.

RESEARCH DIRECTIONS

Much of the nutrition-related research sponsored by the NIGMS pertains to basic research on diseases. The following leads, for example, are being pursued:

- The effects of liver disease and dietary status on the absorption, distribution, and clearance of model pharmaceutical agents.
- The effects of sepsis on the ability of the liver of a critically injured patient to metabolize dietary fat. The findings may serve as a basis for developing better nutritional support for the septic patient.
- Cell surface transport systems that maintain cellular levels of the amino acids necessary for protein syntheses and energy metabolism.
- Adaptive regulation of nutrient transport by the gut. Transport appears to be governed by nutrient-receptor proteins on specific cell surfaces.
- The structure, biosynthesis, and turnover of liver cell surface receptors such as the transferrin receptor and its role during iron uptake.
- Receptors that recognize serum proteins carrying galactosyl sugar residues, including hormones that regulate the rate and extent of nutrient uptake and processing in the liver.
- Membrane structure and function in the liver, including membrane-associated domains of cytochrome P-450, the terminal oxidase of the liver's microsomal metabolizing system.

OUTLOOK

The NIGMS aids in establishing the foundation of new knowledge needed to make advances in the understanding of many diseases. Accordingly, the nutrition-related research it supports will help to provide the concepts and relevant data necessary to remove barriers blocking progress to new treatments, and thereby serve to improve the health of the nation.

For more information on the NIGMS nutrition program, contact:

Yvonne T. Maddox, Ph.D.
Biophysics and Physiological Sciences Program
National Institute of General Medical Sciences
Westwood Building, Room 905
National Institutes of Health
Bethesda, MD 20892
(301) 496-7001

Since the NICHD was created in 1963, its nutrition research program has focused on the continuum of human development, from conception through infancy, childhood, and adolescence. The program emphasizes preventive approaches to nutrition-related conditions and stresses health promotion as well as disease prevention. Much of the research is multidisciplinary in nature and involves the genetic, biochemical, developmental, anthropometric, behavioral, and cultural aspects of nutrition. The NICHD supports research on maternal and fetal nutrition; nutrition during infancy, childhood, and adolescence; the relationship of nutrition to reproduction; behavioral and cultural aspects of nutrition; obesity and its nutritional antecedents; and assessment of nutritional status.

PROGRAM HIGHLIGHTS

The Institute has a strong interest in the nutrient requirements of normal, premature, and low-birth-weight (LBW) infants, as well as in the composition of human milk, cow milk, and synthetic formulas, in relation to optimal infant nutrition. In some of this work, the interest centers on metabolic processes in neonatal adaptation, and on the role played by essential nutrients and other components of human milk. Research on cultural and behavioral determinants of nutritional individuality includes studies of habits, taste, and olfaction; food avoidances; and behavior modification of dietary intakes. Research on nutritional antecedents of adult disease focuses primarily on factors in the development of obesity in infancy, childhood, and adolescence.

Low-Birth-Weight Initiative

In the U.S., the most important factor contributing to the infant mortality rate is a birth weight of less than 2,500 gm, or 5.5 lbs. At present, 6.7 percent of all U.S. babies weigh less than 2,500 gm at birth and are termed LBW infants. In FY 1985, the NICHD inaugurated the Low-Birth-Weight Initiative order to focus more research attention on the nationwide problem of infant mortality and birth-weight-specific mortality. The nutrition component of this initiative is divided into several critically important facets: nutritional management in pregnancy, nutritional management of the very-low-birth-weight (VLBW) infant, and gastrointestinal development.

As part of this initiative, a major effort is now under way to sample over 900 pregnant black women in Washington, D.C., to correlate nutritional, medical, and psychosocial factors with pregnancy outcome. The overall goal is to identify the most significant factors contributing to the incidence of low-birth-weight. Preliminary data analyses show that the following maternal factors correlate significantly with infant birth weight: height; weight gain; and intake of folacin, zinc, and vitamins A and B_6. Ultimately, an intervention study designed to reduce the incidence of LBW in this population will be undertaken.

Vitamin B_6 and Brain Development

The finding that 68 percent of the pregnant women in the study described above had a suboptimal intake of vitamin B_6 could have important implications, since studies of rats fed B_6-restricted diets during gestation and lactation revealed profound brain changes in their progeny. These included a marked increase in the frontal cortex in the concentrations of the tryptophan metabolite 3-hydroxykynurenine. This metabolite is toxic to neuron-derived cell lines in culture, and produced convulsions when injected into the cerebral ventricles of rodents, providing a possible explanation for the convulsions seen in B_6-deficient neonatal animals. Suboptimal B_6 intakes also produced changes in neurotransmitters in other parts of the brain of 4-week-old animals. Though concentrations normalized later, this interference with central nervous system function during a critical period of brain development could have significant long-lasting results.

Human Milk and Infections

Several studies have demonstrated that infants fed human milk have lower rates of gastrointestinal infection than infants fed formula. Apparently, there is interaction between specific constituents of milk and epithelial surfaces of the gastrointestinal tract. Another possible mechanism is the modulation by milk of factors in the infant's immune system, so that increased amounts of protective substances are produced. Preliminary evidence from an NICHD grantee shows that VLBW infants fed fortified human milk excreted in their urine higher levels of almost all antimicrobial protective factors than those fed formula, although serum levels of these factors did not differ between the two groups. These and other observations suggest the presence of a human milk factor that induces the production of mucosal immune substances by these babies.

Vitamin A in Morphogenesis

The formation of a complex structure such as a limb (morphogenesis) requires the coordination of many different processes. These include the differentiation of specific tissues such as bone, muscle, nerves, blood vessels, and skin, the spatial organization of these structures, and their integration into a functional unit. For many years scientists have been trying to identify molecules that are capable of directing morphogenesis. Now a group of NICHD-supported investigators have identified what appears to be the first such morphogen in vertebrates. They have shown that exogenously applied vitamin A can direct the formation of a perfectly shaped secondary limb in a developing embryo, and that this substance exhibits the spatial distribution proposed for such a morphogen. Excess vitamin A, however, has also been shown to disrupt normal development, producing a syndrome of neuroskeletal birth defects in humans. A fundamental question, therefore, is whether vitamin A produces these apparently disparate effects by the same mechanism, or whether different molecular and cellular processes are responsible for them.

In order to answer this question, NICHD-funded laboratories are identifying the biologically active molecular forms of vitamin A and its metabolites during normal limb development and in the production of birth defects. The results indicate that the morphogenetic and teratogenic effects of vitamin A may depend on two different molecules in its metabolic pathway. These studies provide important information about cellular and molecular controls of normal development which may eventually lead to feasible protocols for the regeneration of lost appendages.

RESEARCH DIRECTIONS

The NICHD has begun work with a group of consultants on the development of a new NICHD Five Year Plan for Nutrition Research and Training. The aims of the plan are:

- To identify the global issues in maternal-fetal, neonatal, infantile, childhood, and adolescent nutrition.
- To pose key questions about these global issues, including epidemiologic questions.
- To identify the technology needed to address these key questions.

The plan is expected to have an important influence on the activities supported by the NICHD, providing information needed for the development of areas of emphasis and the allocation of resources for nutrition research within the Institute's programs. Subjects identified for attention thus far in the new Nutrition Research Plan are: nutritional epidemiology and international nutrition, trace elements and micronutrients, nutritional therapy of inborn errors of metabolism, obesity and energy metabolism, feeding low-birth-weight and term infants by enteral and parenteral nutrition, lipoproteins and antecedents of adult vascular disease, nutrient interactions, feeding and gastrointestinal development, maternal-fetal nutrition, fetal growth factors, nutrition and brain development, and human milk research. It is expected that the new plan will be completed in FY 1990.

A few examples of current nutrition research supported by the NICHD are as follows:

- Studies on the effects of vitamins on reproductive function and morphology, and on the relationship between oral contraceptive use, cervical dysplasia, and folate levels.
- Maternal-fetal nutrition research on the mechanisms of placental transfer of essential nutrients and the influence of these nutrients on normal and abnormal fetal development.
- Studies of events governing development of the gastrointestinal tract from fetal life to adulthood. The role of human colostrum and milk in stimulating the development of the gastrointestinal tract and protecting it from disease are of special interest.
- Studies of human milk, cow milk, and synthetic formula to assess the

requirements for optimal growth and development in normal and LBW infants.

- Research on the nutritional antecedents of various adult diseases, including the nutritional ramifications of diabetes in pregnancy for infants born to diabetic mothers; the development of obesity in infancy, childhood, adolescence, and early adulthood; and dietary, genetic, and metabolic precursors of atherosclerosis.
- Studies of behavioral, neurochemical, genetic, and hormonal factors in childhood obesity.
- Studies of the influence of nutritional factors on cognitive development and behavior in both normal subjects and patients with inborn errors of metabolism.

OUTLOOK

NICHD's nutrition research focuses on human development from conception through infancy, childhood, and adolescence. The program emphasizes research on preventive approaches and stresses health promotion as well as treatment.

As progress is made in NICHD-supported laboratories and clinics, the findings become available to improve the outlook for babies born in the U.S. and throughout the world.

For more information on the NICHD nutrition program, contact:

Ephraim Y. Levin, M.D.
Medical Officer
National Institute of Child Health and Human Development
EPN 637
National Institutes of Health
Bethesda, MD 20892
(301) 496-5593

The NEI, which was established in 1968, increased its emphasis on nutrition-related research by appointing in 1982 a special assistant to the director to develop and coordinate this activity. In 1989, an Office of International Program Activities was established, and the NEI Director's special assistant for nutrition-related research was appointed director of this office. From its inception, the nutrition-related research program of NEI has aimed at reducing the prevalence of blindness, visual impairment, and eye disease in the U.S. and throughout the world. As much as 80 percent of the millions of cases of blindness worldwide are considered curable or preventable. For example, xerophthalmia, a potentially blinding vitamin A deficiency disease, is the leading cause of nutrition-related blindness and visual impairment among the world's children.

PROGRAM HIGHLIGHTS

The NEI supports research on the role of general nutrition as well as on specific nutrients--such as vitamins A, C, B_6, and E, protein, copper, and zinc--on normal ocular and visual development, health, and function. NEI-supported scientists are also examining the association between nutritional imbalances and eye and vision disorders, such as cataract, retinopathy of prematurity, retinitis pigmentosa, gyrate atrophy, macular degeneration, and other diseases resulting in blindness.

Vitamin A and the Ability to See and Survive

Xerophthalmia is directly linked to a dietary deficiency of vitamin A. Worldwide, it is estimated that 250,000 to 500,000 children are blinded annually from this preventable cause. The number of children who have their vision impaired by vitamin A deficiency may be 5 to 10 times greater, and an equally large additional group of children are subclinically deficient and may have their general health status compromised, thus contributing to high childhood mortality rates.

Vitamin A, or retinol, plays an important role in the visual process, particularly through the generation of visual pigments. NEI supported investigators are studying the interactions in ocular tissue of vitamin A with other nutrients such as vitamin E, C, and zinc. These scientists are also examining the synthesis, metabolism, and molecular structure of retinol-binding proteins and their function in the eye, because deficiencies of these proteins or alterations in their binding properties appear to compromise the normal functioning of vitamin A in the retina and in the pigment epithelium of dystrophic eyes.

Field-based studies with collaborators in India are attempting to determine the effectiveness of raising the level of vitamin A intake of preschool-age children to the recommended level through a weekly supplement delivered by community workers. The effect of this moderate improvement in vitamin A nutriture on the incidence of ocular, gastrointestinal, and respiratory morbidities is being monitored.

Age-Related Cataract

Cataract is a leading worldwide cause of blindness and visual disability, affecting about 17 million persons in both industrialized and developing countries. By far the most common of the many different kinds of cataract is age-related cataract, which may lead to premature loss of productive potential. Although surgery is an effective treatment, there is no known way of preventing or delaying the onset of age-related cataract.

NEI-sponsored case control studies in the U.S., Italy, and India with similar research designs are investigating possible personal and environmental risk factors for cataract, including diet, disease history, and environmental exposures. These studies are now completed and the data from India have being analyzed. These data suggest that, among several other risk factors, diets low in selected nutrients and a decreased body mass index, can be associated with increased risk of some types of cataract, i.e., better-nourished persons in India may have less risk of cataract. As the data analysis is completed from the other studies, cross-country consistency in nutritional and other risk factors will be evaluated.

Nutrition, Oxidation, and Cataract Formation

NEI intramural scientists are using Royal College of Surgeons (RCS) rats to study the effects of nutrition, oxidation, and other environmental factors such as light intensity or darkness, on the incidence and progression of posterior subcapsular opacities (PSO) associated with retinal degeneration. Oxidative changes in polyunsaturated fatty acids induced by light exposure have been found to lead to formation of aldehydes toxic to lens cells and their membranes. Purified diets containing beta-carotene (an efficient quencher of singlet oxygen) and BHT (an efficient scavenger for secondary oxidized products) have been shown to prevent PSO and mature cataracts.

RESEARCH DIRECTIONS

Among the many nutrition-related research areas supported by the NEI, the following indicate the types of research activities within:

- Investigations of vitamin A, its derivatives, and the proteins that bind it to cells (a major focus of NEI investigation) are progressing. Scientists are exploring the role these substances play in the normal metabolism of ocular tissues and in the visual process. Alterations of ocular tissue integrity and metabolism by chronic deficiency of vitamin A are under study. These studies include investigating the role of vitamin A in maintaining the immune competence of the eye and the ability of ocular tissue to respond to infections and trauma.
- Operations research studies related to the prevention of vitamin A malnutrition, the major cause of preventable blindness among children in the developing world are under way. Epidemiological studies are in progress to identify the nutritional and environmental factors that act with vitamin A deficiency to increase the risk of developing xerophthalmia and keratomalacia, irreversible corneal damage and destruction. Methods for assessing the relative vitamin A status of individuals are being evaluated.
- Studies have been undertaken on the role of vitamins E and C in nourishing ocular tissue and in maintaining visual acuity during natural and induced chronic and acute exposure to oxidants.
- Research is being conducted on cataract and macular degeneration, major causes of visual disability and blindness. The nutrient environment in which cataract and macular degeneration develop, and the potential for altering this environment to prevent or arrest the cataractous and degenerative process, are additional foci of research activity. Deficits of antioxidant nutrients are under particular scrutiny in efforts to clarify the etiology of cataract.
- Research is underway on the fundamental role played by essential minerals--such as zinc, calcium, and magnesium--in lens metabolism and on the consequences of disturbances in mineral balances to eye health. The association between ascorbic acid levels in ocular fluids and the healing process after corneal trauma is also under investigation.
- Several studies are designed to detail the fundamental role of essential minerals, which are a critical in retinal function, in intraocular transport and function. In addition, studies are under way to determine whether dietary modifications may be effective in correcting the biochemical abnormalities associated with gyrate atrophy and other retinal degenerative diseases.

OUTLOOK

Among the eye and vision disorders addressed by the NEI, those with nutritional associations appear highly susceptible to prevention, diagnosis, and treatment strategies. The social relevance and international public health impact of these problems give them particular immediacy.

For more information on the NEI nutrition program, contact:

Barbara A. Underwood, Ph.D.
Assistant Director for International Program Activities
National Eye Institute
Building 31, Room 2B13
National Institutes of Health
Bethesda, MD 20892
(301) 496-4876

In 1966, the Secretary of Health, Education, and Welfare established the Division of Environmental Health Sciences at NIH to attack enviromentally related problems. The Division was elevated to institute status in 1969. To attack environmentally related problems, the NIEHS supports a broad spectrum of biomedical research ranging from basic studies at the cellular and molecular levels to more applied programs aimed at identifying hazardous enviornmental substances and understanding the effects of exposure and the mechanisms by which toxic substances may cause biological damage. The Institute, which has its headquarters in Research Triangle Park, North Carolina, performs research at both its intramural lab and through sponsored research at institutions throughout the U.S. and the world.

During the past year, the American public's concern over chemical contamination of the food and water supply has been at an all time high. News headlines have included stories about terrorist poisoning of grapes, pesticide residues in apples, contaminated drinking water, and chemical contaminants in fish.

Determining the identity and nature of these and other chemical, physical, and biological factors in the environment that might affect human health is at the core of NIEHS research. It is also reflected in the commitment of the Institute to the National Toxicology Program (NTP), a Department of Health and Human Services interagency effort that attempts to fill information gaps about the possible toxicological effects of human exposure to enviromental chemicals. Institute grantees and intramural scientists have utilized this extensive data base of scientific knowledge to facilitate their own research.

PROGRAM HIGHLIGHTS

Intramural and Extramural Studies

As part of an effort to understand the mechanism of action, a grantee scientist discovered a new class of insecticides that has a higher selective toxicity for insects. Such highly selective chemicals could reduce the potential for human toxic effects through food-borne exposure to insecticide residues.

Institute grantees have used laboratory animals to show that chemicals transferred through breast milk can affect neonatal development of liver and reproductive function. In addition, in adult laboratory animals, certain agrichemicals have been shown to contribute to reproductive dysfunction. These and other data suggest a role for agrichemicals as contributing factors in human diseases.

NTP scientists have recently completed a 2-year study of the naturally occurring fungal toxin ochratoxin A, a contaminant in corn, peanuts, cottonseed, dried fish, and nuts. They found that it induced the highest incidence of kidney cancers in animal models ever seen in any National Toxicology Program biological assay.

An early finding from a study of 25 common groundwater contaminants indicated suppressed immune response in mice drinking the water. The mice appeared healthy, but were unusually susceptible to infections.

The drinking water contaminant 2,4-dichlorophenol was evaluated and found to offer no evidence of carcinogenicity in rodents.

In an epidemiological study of 104 healthy women who had been attempting to become pregnant, those who consumed more than one cup of coffee a day were half as likely to become pregnant as were women who drank less.

An NIEHS conference of experts who met to discuss the problem of chemically contaminated aquatic food indicated that certain kinds of water pollution are likely causes of cancers and other diseases in fish. However, except for very fatty fish, the fish eliminate most of the carcinogens by the time they are ready to be eaten. Shellfish often do not metabolize or get rid of pollutants, and may pose more of a health risk.

RESEARCH DIRECTIONS

A number of areas are being explored that hold promise of furthering understanding of the relationship between nutritional factors and human health, including the following research:

- Monitoring and controlling the presence of aflatoxins, a potent liver carcinogen in grain and food products, is hampered by difficulties in applying sophisticated analytical chemistry techniques in the field. Through its small business program, NIEHS is developing sensitive devices for measuring this contaminant in the field.

- A number of studies examining breast milk as a source of chemical exposure are either planned or under way. In Mexico, an NIEHS study is looking at the duration of lactation and illness of children exposed through mother's milk to DDE, a metabolite of DDT. An animal model is being developed for study of offspring exposure to drugs and other chemicals through mother's milk. In the course of this work, the drug Cimetidine, designed to decrease acid secretion in ulcer disease, has been found in the milk of rats in concentrations 25 times higher than in plasma. The mechanism of concentration is still under investigation.
- In July 1989, the Institute held a meeting on the toxicology and human health effects of methyl mercury, a compound found in many lakes that supply fish eaten by Americans. Consumption of methyl-mercury-contaminated fish presents a serious health risk, particularly to children and pregnant women.
- Data analysis is under way in a study examining the biological response among a group of 70 postmenopausal women who have a diet high in plant estrogens.
- NIEHS is planning a conference in November 1989 on the implications for human health of possible changes in the global climate, including assessment of changes in the food supply. In a time of global warming, fungal contamination of grains and other stored foodstuffs are likely to increase dramatically.

OUTLOOK

The NIEHS is devoted to developing knowledge that will protect the environmental health of the world's population. In this connection, the Institute's responsibility for nutritional research will continue to be an important part of the its programs.

For more information on the NIEHS nutrition activities, contact:

Thorsten Fjellstedt, Ph.D.
Deputy Director
Division of Extramural Research and Training
National Institute of Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, NC 27709
(919) 541-0131

Today, approximately 12 percent of Americans are over age 65. By the year 2025, this number is expected to grow to over 20 percent as life span extends well into the eighth decade. The mission of the National Institute on Aging (NIA) is to foster research that finds methods to extend years of productive life through improved health, lifestyle, and psychosocial status. The NIA's Nutrition and Aging Program contributes to this goal by sponsoring basic, animal model, clinical, and population-based studies to determine the ways that nutrition influences the onset and progression of aging.

PROGRAM HIGHLIGHTS

Nutrition and aging research poses several unique challenges. The variation of physiological and behavioral measures increases with age. Since the rate of change in functional capacity and aging processes differs among individuals, those who reach old age are the most biologically heterogeneous of all age groups. The diversity observed in aging subjects results from a lifetime of environmental experiences superimposed on individual differences in genetic predisposition. Investigators in nutrition and aging must consider such factors as genetic variation, race, smoking status, physical activity, health and medication history, and social factors.

A most difficult problem is to separate those changes observed in old age that are due to inevitable aging processes from those that are manifestations of pathology. In some cases, like those related to the progressive loss of skeletal tissue, an aging process becomes pathological when bone density is reduced to a level where low trauma fractures can occur. Researchers must also determine if the magnitude of change in age-related parameters is clinically significant and which aging processes are detrimental to the health of older individuals.

Metabolic Studies in the Baltimore Longitudinal Study of Aging (BLSA)

NIA's Gerontology Research Center in Baltimore, Maryland, has been collecting detailed nutrition information (7-day diet records) from male participants in the BLSA for almost 30 years. These data are being analyzed in relation to aging and development of various age-related diseases. Since 1984, 7-day diet records have been collected from women in the study. Of the 300 7-day records that have been collected, 200 have been analyzed. An average of 44 percent carbohydrate, 35 percent fat, and 16 percent protein were consumed by the women in the study. Cholesterol intake averaged less than 300 mg/day and the women had an average polyunsaturated/saturated fat (p/s) ratio of 0.6. Over 50 percent of the women took some type of vitamin or mineral supplements. For those women who were not taking supplements, calcium, magnesium, zinc, folacin, and vitamin B_6 were most often below the RDA levels.

In conjunction with estimates of dietary intake, a number of biochemical measures of nutritional status are being analyzed. Plasma levels of antioxidant vitamins A and E were measured in about 1,000 subjects. Levels of a provitamin A, beta-carotene, were higher in women than in men, but levels increased with age in both sexes. Levels of preformed vitamin A, retinol, however, were higher in men and not related to supplement intake in either gender. Levels of tocopherol, the most active form of vitamin E, were higher in older people than in younger counterparts and were highest in those taking supplements. Plasma ascorbic acid levels were determined in about 400 men and women. Levels were higher in older people and higher in women than in men. Smokers had slightly lower levels.

Because using a single 24-hour dietary recall is often not adequate to provide information on diet and health relationships, the BLSA group was used to pilot test telephone interview methods directed at collecting 24-hour computerized diet records. These approaches will be used to obtain additional dietary information for the National Health and Nutrition Examination Surveys (NHANES III). Sixty men and women were interviewed once in person and twice more in followup telephone interviews. Length of interview and number of foods reported were analyzed in relation to age and sex. Although the length of interviews decreased significantly after the first interview, no differences in the performance of men and women due to age were observed. The number of foods reported also remained constant between the in-person and telephone interviews. These data suggest the telephone dietary interviews will provide a useful adjunct to information collected from older people in the NHANES III.

Another study measured the efficacy of either normal or high protein, hypercaloric dietary intake on healing of pressure sores in nursing home patients. High protein diets were associated with better healing, especially if the patient had access to air-fluidized beds. Patients with pressure sores required a much higher caloric intake than those without this problem, although they were thinner and more anemic than other comparibly diagnosed nursing home patients. These results show the need to maintain good nutritional status in this population.

In a different type of study, dietary intakes of senior athletes were compared to BLSA controls matched for age and body mass index (BMI). The athletes, ages 58-77, had a higher aerobic capacity and lower percent body fat than BLSA controls. They consumed more calories and protein per kg body weight and had a lower percentage of calories from fat than the controls. These results suggest that habitual aerobic exercise can mediate changes in dietary intake and body composition associated with aging.

Nutrient Requirements in Older People

In order to understand how nutrition supports good health and helps to maintain function in old age, it is important to identify the ways nutrients may influence tissues and organ systems. Also, the question arises as to what relationships exist between dietary components and age-related diseases. Despite a paucity of information regarding the age-specific nutritional requirements of older people, significant progress is being made in a number of nutrition and aging research studies, including those investigating the absorption and metabolism of lipids.

In animal models, aging is associated with increased intestinal capacity to absorb lipids; notably vitamins A, D, and E, and mono- and polyunsaturated fatty acids.

The unstirred water layer (UWL) in the small intestine helps control the absorption rate of lipids. The greater surface area and thinner water layer that occurs with age decreases the resistance to lipid absorption. Based mainly on animal studies, some investigators hypothesize that this age-related increase in intestinal absorption of fats may be an adaption of the bowel to decreased pancreatic and hepatic digestive function. Protein and carbohydrate absorption that are not regulated by the UWL do not increase with age.

Lipids are absorbed by passive diffusion with rapid accumulation of triglycerides by brush border membranes and the lumen of the vesicles. Vitamin E absorption shifts from portal to lymphatic transport with age. Although vitamin D transport does not appear to be compromised during the aging process, some older people have a lower vitamin D status. Older women, who are at highest risk, have a higher potential for urinary calcium loss, lower serum levels of 25-hydroxy vitamin D, and a lower potential for synthesizing vitamin D, due in part to less exposure to sunlight. These are factors that may contribute to the higher incidence of osteoporosis in older women.

Nutritional Status in Older People

Except for certain subgroups such as the economically disadvantaged and chronic alcoholics, epidemiologic evidence indicates that clinical undernutrition is uncommon in the majority of free-living older people in the United States (less than 5 percent of NHANES subjects over 50 years). Although the majority of older people are not undernourished, they represent a particularly vulnerable segment of the population. Studies have shown that even in the absence of clinical deficiency symptoms, the average serum levels of some nutrients such as vitamin D and folate are lower in older age groups than in younger persons (less than 50 years of age). These differences may be responsible for subclinical deficiencies or reduced body stores that increase their vulnerability to intercurrent illness or to the chronic diseases of old age.

Recent evidence also suggests that age-related changes in body composition are related to nutritional and health status of older people. In many mammalian species, there is a loss of lean body mass and a decrease in total body water accompanying an increase in body fat. This proportional change from lean body mass to fat can change the basal metabolic rate, lowering the need for energy. These changes involve alterations in hormonal control and in complex metabolic regulatory systems. In humans, adipose tissue increasingly tends to distribute in the trunk and around vital organs. In women, there appears to be a postmenopausal acceleration of this trend but the waist-hip ratio is distinctly higher in men. The sex difference in waist to hip ratio is due to differences in waist circumference; changes in women occur in both the hip and the waist while in men the waist changes but hip size remains about the same. Overall, BMI and waist-hip ratio are highly correlated.

Using BMI as a measure of obesity, mortality in older people increases at both the low and high end of the scale with an upward shift in optimal BMI with age. Longitudinal studies show that over a period of 10 years, in those 55 to 74 years at baseline, male mortality decreased with increasing BMI except for the morbidly obese. No such association was found in women. These data were adjusted for the effects of related factors such as blood pressure, smoking, socioeconomic status, and diabetes. In cross-sectional analysis, male smokers weigh less and have a lower BMI than nonsmokers. Male smokers also have a significantly higher waist-hip ratio than nonsmokers. Those who begin smoking lose weight but increase their waist-hip ratio, enhancing their health risk.

Severe signs of malnutrition are apparent in many older persons requiring hospitalization and/or the services of long-term care facilities. There is increasing recognition of a syndrome in this group of unexplained rapid weight loss and emaciation, usually associated with an unexplained decrease in food intake. This cluster of symptoms has the characteristics of protein-calorie malnutrition. Protein-calorie malnutrition (PCM) is being diagnosed more frequently among hospital patients, especially in the oldest age groups. The incidence of PCM among those 65 years and older is between one-third and two-thirds of those admitted to acute care facilities. Furthermore, the rate of malnutrition increases with the length of stay. The NIA is encouraging further research on the pathogenesis of this form of PCM to determine whether it represents a syndrome in its own right or occurs secondary to disease.

Energy Restriction in Animals--A Probe into Mechanisms of Aging

In rodents, energy intake restriction without essential nutrient deficiency extends maximum life-span, retards the onset of many spontaneous late-life diseases, and slows the rate of biological aging. Because caloric restriction has been the only intervention that has consistently produced these outcomes, investigators in several areas of basic biology such as peroxidation/free radicals and intermediary metabolism are using this model to test hypotheses about basic mechanisms of aging. Linking energy restriction to longevity may include changes in energy metabolism, gene expression, neuroendocrine regulation, and immune function. Another issue to be resolved is whether this effect seen in rodents and several other animal models applies to primates.

A project at the Baltimore GRC is attempting to determine whether a 30 percent calorie reduction in the ad libitum diet of rhesus and squirrel monkeys can affect the aging rate of a number of physiological, biochemical, and behavioral systems. Two years into the study, preliminary analysis indicates measurable changes in the restricted rhesus monkey compared to the ad libitum controls of similar age. Most notable of these are changes in indices of bone remodeling, albumin levels, and globulin ratios. Age-related decreases in concentrations of lymphocytes and several enzyme levels were observed in the calorie-reduced animals of both monkey species.

Nonenzymatic Glycosylation (Glycation)

Cross-linking of long-lived proteins such as collagen and eye lens crystallins increases as a function of age in both animals and humans and may be responsible for some of the physical changes that occur in aging. A characteristic change associated with age is stiffening or rigidity of some tissues which may be caused by cross-linking collagen and elastin. There is evidence that a process called glycation, or the nonenzymatic reaction of a reducing sugar like glucose to link with an amino acid to form a Schiff base, also affects other tissues and protein products, including enzyme systems.

Although evidence of glycation in biological systems has been well established, it has been difficult until recently to demonstrate its physiological effects and clinical significance in animals and humans. Fluorescent advanced glycosylation end (AGE) products can be used as markers of glycosylation activity to determine the *in vivo* importance of glycation and assess its role in complications of diabetes and aging. "Peptide P," a pyrimidine compound, is being used as such a marker.

Peptide P has been identified and quantitated in human skin obtained at autopsy. It was found that peptide P increases not only linearly with age but exponentially towards the end of the life-span. Peptide P has also been found in crude preparations of aorta, tracheal cartilage, kidney medulla and cortex, liver, heart, and red blood cells.

In addition to demonstrating the synthesis of AGE products *in vivo*, new research shows that there appear to be mechanisms for the removal of AGE products that accumulate in long-lived proteins. A macrophage/monocyte receptor was found that recognizes and internalizes glycated proteins. This removal system is a unique clearance mechanism for senescent proteins *in vivo*, since AGE formation reflects a time-dependent equilibrium reaction that is determined by the amount of reducing sugar present. The efficacy of this system appears to decrease with age. A greater than twofold decrease in both receptor number and binding affinity of AGE receptors has been demonstrated in old vs. young mice. Therefore, aging may enhance tissue damage by preventing the removal of cross-linked glycated proteins.

Age-related Changes in the Chemical Senses

With increasing concern about the nutrition status of older people has come an increased interest in changes in their chemosensory function. According to recent evidence from anatomic, electrophysiologic, and psychosocial studies, both taste and smell decline with age. For example, psychophysical studies of the gustatory system have demonstrated age-related elevation in the threshold of some, but not all, taste and smell stimuli. The role of this change in an individual's perception of real-world foodstuffs is a matter of current speculation. More than half the population over age 65 show some degree of impairment of odor recognition. Furthermore, chemosensory preference for foods that may have different nutrient patterns from those preferred at a younger age, raises the question of a possible relationship between nutritional and chemosensory status.

Osteoporosis and Aging

Although the fundamental pathogenesis of osteoporosis remains unclear, clinical evidence suggests that there are two types of the syndrome. Type I, which occurs mainly in women up to 20 years after menopause, is manifested by vertebral crush fracture and Colles' fracture of the distal forearm. Type II osteoporosis occurs in both men and women over the age of 70 and is associated mainly with hip, pelvic, proximal femur, and wedge type vertebral fractures.

Clinically, type I and II are not readily distinguishable and both often occur in the same patient. However, there are a number of characteristics which help to distinguish them. Type I osteoporosis is associated with excessive and disproportionate loss of trabecular bone, but the rate of cortical-bone loss is only slightly above usual age-related rates. It is also closely related to factors associated with menopause, and the most effective method to date of reducing postmenopausal bone loss is estrogen therapy.

In the type II form of osteoporosis, bone loss is proportionate for both cortical and trabecular bone and is only slightly greater for patients with fracture than for the remainder of the aging population. As bone is lost, increasing numbers of older people have bone densities that fall below the fracture threshold. Age-related risk factors include decreased osteoblast function and impaired 1,25(OH)2D, leading to decreased calcium absorption and secondary hyperparathyroidism. At present, there is no established universally effective therapy for type II osteoporosis.

RESEARCH DIRECTIONS

A concerted effort has been made during the past year to expand the NIA's Nutrition Program. A key task in the expansion plans was to develop a rationale for research priorities. The NIA solicits input from the scientific community to aid in identifying the most important topic areas and directions for nutrition and aging research.

With this in mind, the NIA and the National Institute on Diabetes and Digestive and Kidney Diseases (NIDDK) issued a joint request for application (RFA) to support conferences on nutrition and metabolic factors related to aging. Conference awards were made to cover a wide range of topics:

- Mineral homeostasis in aging people.
- The role of folate and vitamin B_{12} in neurologic function.
- Assessment of nutritional status, measures, and techniques appropriate for older populations and individuals.
- Oral function and nutrition in older people.

- Nutrition in aging blacks.
- The role of glycation in aging and diabetes.
- The relationship of atrophic gastritis and hypochlorhydria to aging.
- Changes in nutrition and chemical senses during aging.
- The use of germfree rats in studies of energy restriction and longevity.

Present research directions and areas of research priority in nutrition and aging are based on NIA staff evaluation of current research, advice from scientific advisors, and the results and recommendations from the nutrition and aging conferences. These include:

- Nutrient requirements and their age-dependent changes in older persons and animal models.
- Effects of age on physiological processes through which nutrients, drugs, and other nonnutrient substances are absorbed, metabolized, and excreted in humans and in analogous animal models.
- Effects of calorie reduction and of caloric excess resulting in obesity on longevity and age-related pathology.
- Nutritional factors associated with physiologic changes such as immunocompetence, neurologic function, body composition, sensory perception, control of appetite, macronutrient storage and utilization, rheology, and otolaryngology, endocrine control, and genetics.
- The role of nutrition factors in prevention and treatment of age-related degenerative diseases, including diabetes, osteoporosis, neurologic disorders, immune deficits, heart disease, cancer, and gastrointestinal diseases.
- Psychosocial aspects of nutrition, including studies of diet as a major factor contributing to the quality of life and how diet interacts with other life style variables, including exercise, smoking, and consumption of alcoholic beverages.
- Nutritional status of older Americans and special subpopulations of older people at special nutritional risk.
- Educational methods and program strategies that best promote adequate food consumption by older people.

OUTLOOK

A rapidly aging population makes it critical to find ways to maximize the span of good health and thereby improve the quality of life of older people. Nutritional factors hold great promise for realizing this goal. For these reasons, NIA's Nutrition Program supports research to clarify nutrition-aging interactions.

For more information on the NIA nutrition program, contact:

Ann Sorenson, Ph.D
Director, Nutrition Program
Geriatrics Branch
National Institute on Aging
Building 31, Room 5C27
National Institutes of Health
Bethesda, MD 20892
(301) 496-1033

NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

In 1950, major arthritis research programs were established within the National Institute of Arthritis and Metabolic Diseases through the Omnibus Medical Research Act. The research programs of the Institute evolved over the decades and its name eventually became the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) in 1980. The Health Research Extension Act of 1985 reestablished the programs of the NIADDK as two institutes: the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the National Institute of Diabetes and Digestive and Kidney Diseases.

The NIAMS conducts and supports basic and clinical research on many of the most debilitating diseases affecting the U.S. population. These include the many forms of arthritis and numerous diseases of the musculoskeletal system and the skin, as well as research on the normal structure and function of joints, muscles, bones, and skin. Basic research involves a wide variety of scientific disciplines, including immunology, genetics, molecular biology, biochemistry, physiology, virology, and pharmacology. Clinical research addresses the fields of rheumatology, orthopedics, bone endocrinology, sports medicine, and dermatology. The NIAMS supports nutrition research related to these disease areas, scientific disciplines, and clinical fields.

PROGRAM HIGHLIGHTS

Current nutrition-related research efforts include examination of associations between diet and bone loss, osteoporosis, and fractures; identification of nutritional factors that may prevent or slow the progression of osteoporosis; assessment of the relationship between obesity and osteoarthritis; and the study of the treatment of various skin conditions with vitamin A derivatives.

Osteoporosis and Nutrition Research

Osteoporosis, a "porous bone" disease, affects an estimated 24 million Americans and causes approximately 1.3 million fractures per year among those 45 or older. The NIAMS has several research efforts under way that focus on the etiology, treatment, and prevention of osteoporosis, including the nutritional aspects of this national health problem.

Osteoporosis is the major skeletal disease in which nutrition appears to play a role. Characterized by bone loss often so severe that minimal trauma leads to fractures, osteoporosis may be classified into primary and secondary forms. Primary osteoporosis, specifically involutional osteoporosis, may occur in two types: type I, postmenopausal osteoporosis, which occurs in women when estrogen levels decline after menopause; and type II, age-related osteoporosis, the inevitable loss of bone mass that occurs in both men and women. Secondary osteoporosis may develop at any age as a consequence of endocrinologic and gastrointestinal conditions or metabolic disorders.

Significant advances in measuring bone density by noninvasive methods have enhanced scientists' ability to diagnose and monitor osteoporosis. These improved methods involve dual-photon absorptiometry, computerized tomography, and dual-energy x-ray absorptiometry.

The nutritional controls of bone mineralization have yet to be identified fully. At present, the only established nutritional determinants of bone mineralization are calcium, phosphate, and vitamin D. According to evidence presented at the 1984 NIH Consensus Development Conference and the 1987 NIH Scientific Workshop on Osteoporosis, postmenopausal estrogen therapy appears to be the primary method for preventing bone loss and fractures in women. These conferences suggested that increased calcium in the diet may slow bone loss in women, especially premenopausal women, but the role of dietary calcium deficiency in causing osteoporosis requires clarification and additional research. The conferees cited calcitonin and sodium fluoride as other agents that may have potential therapeutic value and require further investigation.

Bioavailability of Calcium

There is general agreement that the best natural source of calcium is dairy products, where the "bioavailability"--the amount of calcium absorbed and used by the body--is established. Institute grantees have recently conducted studies to determine the adequacy of spinach, another reportedly good source of calcium, for meeting calcium requirements. Unexpectedly, they found that absorption of calcium from spinach averaged only 5 percent, as compared to 28 percent from milk. The reduced absorption of calcium from spinach is thought to be due to the fact that spinach contains oxalate, a chemical that binds to calcium and makes this calcium salt less absorbable from the intestines than other calcium salts. The NIAMS supports research to determine the optimal intake of calcium, including the bioavailability of calcium from different food sources.

Vitamin D Metabolism

Vitamin D is important in the mineralization of bone. Vitamin D is either produced in the skin by the action of sunlight or it is ingested, most often in the form of vitamin D fortified milk. It is transported to the liver in the form of vitamin D_3 (also called cholecalciferol) by the blood. The liver metabolizes vitamin D_3 to 25-hydroxyvitamin D_3. This product passes into the circulation, reaching other cells which metabolize it further. The kidneys are the most important metabolic tissue in this regard. In the kidneys, 25-hydroxyvitamin D_3 is converted to 1,25-dihydroxyvitamin D_3, which is an active form of vitamin D, and 24,25-dihydroxyvitamin D_3, which is relatively inactive.

Ultraviolet Radiation of the Skin and Vitamin D

At the National Institutes of Health Consensus Development Conference on "Sunlight, Ultraviolet Radiation and the Skin," consideration was given to the role of sunlight for producing vitamin D_3. It was noted that aging significantly decreases the capacity of the skin to produce vitamin D_3. This is significant as members of the elderly population tend to spend less time outdoors than younger individuals and also tend to consume less than the recommended daily allowance of vitamin D. This is compounded by a tendency toward lactose or milk intolerance in the elderly which may result in abdominal discomfort or cramping, and loose stools or diarrhea.

Sunscreens were recommended at the conference for protection from damage to the skin induced by sunlight. As sunscreens have been shown to impair vitamin D_3 synthesis by the skin, nutritional supplementation of vitamin D was recommended for those who use sun screens regularly.

Vitamin D Transport

A major carrier of vitamin D compounds in the blood is vitamin D binding protein, a 56,000 to 58,000 kD molecular weight alpha-2-glycoprotein. Scientists have immunized mice with human vitamin D binding protein, so that they would produce antibodies against the protein. Using purified antibodies, they found the vitamin D binding protein hidden in the membranes of circulating monocytes, one of the white blood cells involved in immunity. Furthermore, it has been suggested that vitamin D binding protein may be involved in the binding of immunoglobulin G to cells.

Besides vitamin D binding protein, several other blood proteins have been implicated in the transport of vitamin D. The influence of various carrier proteins on the uptake of vitamin D by the liver is being studied. These additional carrier proteins include albumin, chylomicrons, chylomicron remnants, low density lipoprotein (LDL), and high density lipoprotein (HDL). Hepatic uptake was found to be greatest when vitamin D_3 was presented on LDL or chylomicron remnants and least on vitamin D binding protein. These results imply a significant role for LDL and chylomicron remnants in presenting ingested and skin derived vitamin D_3 to the liver.

Vitamin D and Bone

It is known that bone cells metabolize 25-hydroxyvitamin D_3 to 1,25-dihydroxyvitamin D_3 and 24,25-dihydroxyvitamin D_3. It has been demonstrated that the enzyme systems catalyzing the synthesis of these vitamin D derivatives are regulated by the derivative products and not by vitamin D_3 itself. These enzymes were found to have relatively short half lives of about 5 hours.

Vitamin D Receptor

Vitamin D can be considered to be a hormone because it is produced endogenously in the skin and acts by binding to receptors on distant cells. Vitamin D receptors have been found not only in the target tissues of bone, the gastrointestinal tract, and the kidneys, but also to have a widespread distribution involving most vertebrate cell types. Evidence has accrued for multiple roles of vitamin D, including effects on the immune system. Researchers have shown that the presence of 1,25-dihydroxyvitamin D_3 significantly increases the activity of messenger RNA in certain lymphocytes, indicating receptor autoregulation.

The effects of 1,25-dihydroxyvitamin D_3 receptor modulation of a human myeloma cell line have also been studied. Myeloma is a form of tumor that involves the antibody producing cells of the immune system. One of the complications of this cancer is the production of a secondary form of osteoporosis. It has been found that 1,25-dihydroxyvitamin D_3 changes the molecules expressed on the surface of the myeloma cell line. There is enhanced expression of some molecules and decreased expression of others. In addition, the bone resorbing activity of these myeloma cells is significantly reduced after treatment with 1,25-dihydroxyvitamin D_3.

The actions of 1,25-dihydroxyvitamin D_3 have been studied using a rat osteosarcoma (a form of bone cancer) model. Rat osteosarcoma cells become more sensitive to 1,25-dihydroxyvitamin D_3 stimulation of calcium uptake with increasing cell culture density. A biphasic response of these cells to 1,25-dihydroxyvitamin D_3 has been observed: low concentrations stimulate and high concentrations inhibit calcium uptake by these cells. Daily injections of 1,25-dihydroxyvitamin D_3 into mice that have been inoculated intracutaneously with rat osteosarcoma produces increased plasma calcium levels and increased tumor mass. In animals inoculated with melanoma cells, which have few or no vitamin D receptors, there was no distinct effect on tumor weight.

Treatments for Osteoporosis

Despite all the evidence of the importance of vitamin D in bone metabolism, its role in the prevention and treatment of osteoporosis is still unclear. For example, in a randomized, double-blind clinical trial involving 86 women, 1,25-dihydroxyvitamin D_3 was not found to be effective in the treatment of postmenopausal osteoporosis.

Effects of Aluminum on Bone

Aluminum tends to inhibit bone formation in humans and animals. In a study of children undergoing dialysis for kidney failure, the bone formation rate was decreased by phosphate binding agents which contained aluminum. Similarly, patients receiving total parenteral nutrition therapy showed multiple abnormalities of bone histology; however, only the patients with associated aluminum deposition in bone showed a decreased rate of bone formation.

Obesity and Osteoarthritis

Osteoarthritis, or degenerative joint disease, afflicts more than 16 million Americans. Osteoarthritis primarily affects cartilage, the protective material that covers and cushions the ends of the bones, causing the cartilage to fray, wear, ulcerate, and in extreme cases, to disappear entirely, leaving a bone-on-bone joint. Osteoarthritis results from a combination of stress on the joints and other unknown factors. It is far more common than rheumatoid arthritis, but usually it is less damaging. Obesity aggravates the condition and may be a risk factor for onset. Obesity has been shown to be an important risk factor for symptomatic knee osteoarthritis and may be more important in women than in men.

Studies of Vitamin A Analogs

Retinoids, compounds related to vitamin A, are a highly promising group of agents that have received widespread recent attention and use in Europe and the U.S. as potential anti-wrinkle therapy. Retinoids have many other applications in the treatment of skin diseases and are being investigated as potential treatments for arthritis. They have been approved by the Food and Drug Administration for treatment of severe cystic acne. The NIAMS Skin Diseases Program has several studies under way and planned to evaluate the therapeutic efficacy and potential side effects of retinoids.

RESEARCH DIRECTIONS

The NIAMS supports programs of research and research training in the fields of arthritis, musculoskeletal diseases, muscle biology, and skin diseases. Examples of nutrition research in these fields supported by the NIAMS are as follows:

- Studies to determine the optimal intake of calcium and the role of exercise in the development and maintenance of strong, healthy bones; for attaining a maximum adult peak bone mass; for minimizing the rate of bone loss in older individuals; and for prevention of osteoporosis.

- Investigations to elucidate the function of vitamin D metabolites alone and their interactions with other factors to control the complex metabolism of bone.
- A clinical trial of the use of fluoride as a treatment for osteoporosis. The clinical endpoint of this investigation will be a comparison of fracture incidence in fluoride versus placebo groups.
- Research to determine functional relationships between essential fatty acid deficiency and skin conditions such as abnormalities of desquamation (normal loss of bits of outer skin in scales) and defects in the skin's water barrier.
- Research projects on vitamin A and its synthetic derivatives, the retinoids. Clinically, pharmacologic doses of vitamin A or other retinoids have been used to treat conditions such as acne, psoriasis, and some forms of skin cancer. Basic research on the mechanisms of action of these agents is being supported toward the development of additional clinical applications.
- Research to evaluate the efficacy of vitamin C in reducing the progression of arthritic lesions of cartilage. Initial studies in cartilage cultures and in experimental models of osteoarthritis have demonstrated a significant influence of pharmacologic doses of vitamin C.
- Studies of the effects of fatty acids and lipid metabolism on the differentiation of keratinocytes (skin basal cells).
- Studies of the effects of aluminum on bone formation and osteoporosis.
- Research on the photobiology of vitamin D.
- A clinical trial of omega-3 fatty acid on the course of rheumatoid arthritis.
- Support of arthritis, osteoporosis and skin disease aspects of the Third National Health and Nutrition Examination Survey through an interagency agreement with the National Center for Health Statistics.

OUTLOOK

The Institute's programs are organized to respond to public health needs as well as to the research opportunities and needs identified by working scientists in the academic community.

The NIAMS also enjoys a strong partnership with several private voluntary agencies dedicated to control of relevant diseases. The concerted national effort that these forces bring into play will ensure continued progress toward more effective methods of treating and perhaps preventing these chronic diseases.

For more information on the NIAMS nutrition program, contact:

Stephen P. Heyse, M.D., M.P.H.
Director
Office of Disease Prevention, Epidemiology, and Clinical Applications
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Building 31, Room 4C13
National Institutes of Health
Bethesda, MD 20892
(301) 496-0434

DIVISION OF RESEARCH RESOURCES

The DRR was established in 1962 and continues to administer programs that develop and ensure the availability of the resources essential to the efficient and effective conduct of human health research. Three Division programs focus on shared resources: the General Clinical Research Centers Program, the Animal Resources Program, and the Biomedical Research Technology Program. The Minority Biomedical Research Support Program and the Research Centers in Minority Institutions Program are designed to strengthen biomedical research efforts at minority institutions. The Biomedical Research Support Grant Program provides flexible funds to institutions heavily engaged in Public Health Service-supported research. The research supported by the institutes and DRR, conducted through all of these programs, span the spectrum of NIH research activities.

PROGRAM HIGHLIGHTS

The DRR develops and supports resources providing access to the latest biotechnology advances from the physical sciences and engineering; general clinical research centers specializing in clinical research within hospitals; and animal resource projects involving more effective use of animals in research. The DRR also funds seven national Primate Research Centers and a number of unusually valuable animal colonies.

General Clinical Research Centers

The General Clinical Research Centers (GCRCs) are 78 specialized clinical research units, usually associated with a medical school or large hospital. The GCRCs provide clinical research resources for investigators supported by the categorical institutes of the NIH or by other peer-reviewed sources of funding. Resources include patient care facilities, with appropriate nursing and dietary support, and sophisticated laboratory technologies, including computer hardware and software.

The GCRCs are used for multicenter trials supported by other NIH institutes such as the Diabetes Control and Complications Trial supported by the NIDDK. Nutrition research at the GCRCs has led to new knowledge about the role of nutrition in obesity and in hypertension; nutritional management of plasma lipid disorders; better nutrition for premature infants; and new nutritional therapy for inborn errors of metabolism. Recent results from the GCRCs include the implication of prostaglandins as mediators of the glomerular hyperfiltration (which accelerates the progression of chronic renal disease) induced by a high protein diet; the demonstration of high fecapentene-12 excretion (which may be associated with increased risk of colon cancer) on consumption of a high fat diet, which was reduced on addition of fiber to the diet; and the use of stable isotope methodology to measure gastrointestinal absorption of various minerals by LBW infants, to develop better infant feeding formulas.

RESEARCH DIRECTIONS

The following are examples of DRR's nutrition-related research support:

- Studies using nonhuman primates as a model for nutrient absorption and investigations on the importance of particular nutrients throughout the life cycle.
- Investigations on low and high density lipoprotein metabolism and the differences that occur as a result of varying types and levels of dietary fat, including fish oils.
- Inquiries into dietary factors in the management and prevention of hypertension, atherosclerosis, osteoporosis, and coronary heart disease.
- Studies on the nutritional value of human milk and of breastfeeding; development of milk formulas for normal, premature, and LBW infants.
- Studies of the regulation of gastric secretion by peptide hormones.
- Research on nutritional and metabolic factors in the treatment of diabetes, hepatitis, pulmonary and renal disorders, and inborn errors of metabolism.
- Investigations on the pathogenesis of obesity, including genetic, gestational, behavioral, and hormonal factors influencing weight gain and weight loss.
- Studies on nutritional assessments, dietary modifications, and parenteral nutrition in patients with cancer of different body sites.

OUTLOOK

The DRR will continue to support resources essential to the conduct of biomedical research, which will lead to improved human health.

For more information on the DRR nutrition program, contact:

Bernard Talbot, M.D., Ph.D.
Medical Officer
General Clinical Research Centers Program
Division of Research Resources
Westwood Building, Room 10A03
National Institutes of Health
Bethesda, MD 20892
(301) 496-6595

Established in 1956, the DRS provides veterinary resources, biomedical engineering and instrumentation, comprehensive research library facilities, and medical arts and visual communication systems in support of NIH research, including support of nutrition research.

PROGRAM HIGHLIGHTS

Facilitating many aspects of research by categorical and disease-focused research by the institutes, DRS plays a significant role in NIH's scientific program, including nutrition-related research.

Veterinary Resources Branch

The Veterinary Resources Branch (VRB) provides professional and technical support services related to the care and use of animals, including the provision of animals, research holding, consultation, and disease control services.

The VRB's program in laboratory animal nutrition was established in order to improve the overall status of animal colonies associated with NIH research. VRB developed well-defined "open formula" diets, the so-called "NIH diets" with precisely defined ingredient and nutrient compositions, which are now used in animal colonies at the NIH, throughout the U.S., and by the international biomedical research community. Their primary advantage is their ability to enable investigators to eliminate nutritional status as an experimental variable. There is also an economic advantage to the NIH in using these diets--an estimated 30 percent reduction in cost, compared with procuring commercial diets on a sole-source basis.

The nutrition program has established quality assurance procedures for all animal feeds purchased under NIH contracts. Major elements of that procedure include the

Table 3. Small Animal Models with Applications for Nutrition-Related Research

Small Animal Model	Name	Application
Mice	Dwarf (dw)	Deficiency of growth hormone
	Yellow (a*vy)	Obesity
	NOD/N	Nonobese diabetes
	Various inbred strains	Wide range of body weights
Rats	SHR/N	Hypertension
	SHRSP/A3N	Hypertension and cerebral infarction
	N:BHE	Mild disorder of carbohydrate metabolism
	WBB/1N	Insulin-dependent diabetes mellitus
	Corpulent (cp)	Obesity
	LA/N-cp	Hyperinsulinemia without diabetes; normotensive
	SHR/N-cp	Hyperinsulinemia and diabetes; hypertensive
	WKY/N-cp	Hyperinsulinemia and diabetes; normotensive
	RHAIN-J	Jaundice-hyperbilirubinemia
	ACI/N-J	Jaundice-hyperbilirubinemia
Rabbits	Watanabe Heritable Hyperlipidemic (whhl)	Familial hypercholesterolemia

development of standards and specifications for manufacturing facilities and diets; site inspections of facilities associated with manufacture, warehousing, and transport of diets; and assays of diet samples for nutrients and potential contaminants.

The collection of small laboratory animals kept as a genetic resource currently totals approximately 300 closed breeding colonies of rodents and rabbits. This collection contains animal models for studying human disease in most disciplines of biomedical research. The animal models of most interest to nutrition-related research are presented in table 3.

RESEARCH DIRECTIONS

DRS scientists collaborate in animal nutrition programs; they work with many scientists at the NIH and other institutions. Recent and current collaborations include the following projects:

- Investigations by the NIA to determine the influence of a calorie-restricted diet on the longevity of nonhuman primates.
- Long-term toxicology research by the NIEHS that requires a specially developed diet for the long-term maintenance of rodents.
- Research by NASA to develop rodent diets that can be used effectively in a zero-gravity environment.
- Studies at Georgetown University on the influence of various dietary constituents on hypertension in the spontaneously hypertensive rat.

OUTLOOK

The DRS will continue to play an important role in the nutrition research programs of the NIH and beyond, serving as an adjunct and facilitator whenever laboratory animal standards are essential for reliable research outcomes.

For more information on the DRS nutrition-related program, contact:

Joseph Knapka, Ph.D.
Small Animal Section
Veterinary Resources Branch
Division of Research Services
Building 14A, Room 109
National Institutes of Health
Bethesda, MD 20892
(301) 496-4481

JOHN E. FOGARTY INTERNATIONAL CENTER FOR ADVANCED STUDY IN THE HEALTH SCIENCES

Established in 1968, the Fogarty International Center supports fellowships to enable U.S. and foreign scientists to pursue their research interests in U.S. and foreign laboratories, providing an opportunity for them to exchange information and research experiences.

PROGRAM HIGHLIGHTS

International Research Fellowship Program

Four foreign postdoctoral fellows are conducting nutrition research in U.S. laboratories in vitamin D deficiency and bone fractures, nutritional supplementation and placental and fetal growth, glutamine-enriched diets and regeneration of intestinal mucosa, and statistical verification of nutrition questionnaires.

For more information on the FIC programs in support of international research programs and fellowships, contact:

Mr. James A. Bryant
Public Affairs Officer
Fogarty International Center
Building 16, Room 210
National Institutes of Health
Bethesda, MD 20892
(301) 496-8098

NATIONAL CENTER FOR NURSING RESEARCH

The National Center for Nursing Research (NCNR), established in April 1986 as an NIH component, supports research in nutrition as it relates to health promotion, disease prevention, and acute and chronic illnesses and disabilities. The goal of nursing research is to improve nursing care for all segments of society by expanding the scientific base for nursing practice, focusing on the full spectrum of human health and disease, from the prenatal stage to old age.

PROGRAM HIGHLIGHTS

Current NCNR nutrition highlights are primarily in infant health, in health promotion, and in obesity as a major health threat.

Infant Health

The nutritional implications for infants begin with the nutritional health of their mothers prior to birth. One NCNR study is directed toward identifying maternal health behaviors during pregnancy as they relate to pregnancy outcome. Two other studies follow the growth and development of infants after birth and measure their nutrition status.

Health Promotion

Nutrition is one of a number of health promotion behaviors being examined in a variety of populations. A group of adolescents is being studied to identify health compromising behaviors, including poor nutritional habits. Adults at risk for health problems such as cardiovascular disease and skin breakdown, which would include ulcers or lesions, are being studied to identify the nutritional behaviors related to health status. The impact of nutrition on premenstrual symptoms in women is also being examined.

Obesity

Many obese Americans face curtailed life expectancy and the prospect of developing a major disabling or fatal disease. The NCNR is supporting studies that examine the genetic, metabolic, clinical, environmental, and behavioral aspects of obesity in animal models; define types of obesity; and establish better methods of prevention and treatment. Recent studies on weight gain after weight loss have led to new information on the complex interactions of the body's systems controlling energy intake and energy expenditure. The NCNR is supporting research on behavioral patterns conducive to weight control by testing the effectiveness of self-management strategies.

RESEARCH DIRECTIONS

The NCNR has developed the research structure needed to make progress in priority areas that address specific health concerns of society. The nursing research priority areas with nutrition research potential include:

- Nutritional measures that will control weight loss and maintain a nutritional balance in persons who have AIDS/ARC.
- Improved feeding techniques for low-birth-weight infants to provide needed nutrition and support weight gain.
- Assessment of nutritional needs and related issues in elderly persons who require long-term care.

OUTLOOK

The challenge that lies ahead for the NCNR's nutrition program is to encourage a strong research environment that will produce the scientific knowledge needed to guide nursing practice. Future studies will build on the basic sciences, integrating them with the biological, behavioral, and social correlates that influence nutritional health and disease. Collaboration with other NIH components is of continuing importance.

For more information on the NCNR nutrition program, contact:

Moira Shannon, Ed.D., M.S.N.
Nurse Consultant
Health Promotion and Disease Prevention Branch
National Center for Nursing Research
Building 31, Room 5B13
National Institutes of Health
Bethesda, MD 20892
(301) 496-0523

Section 3. Highlights of the NIH Biomedical Research Programs on Nutrition

HIGHLIGHTS OF THE NIH BIOMEDICAL RESEARCH PROGRAMS ON NUTRITION

The NIH's nutrition research programs typically include both an extramural and an intramural component. The intramural program is conducted primarily within NIH laboratories, clinics, and administrative facilities. Many of them are located in Bethesda, Maryland, a few miles from the nation's capital. In addition to the nutrition research of institute scientists in NIH laboratories and clinics, NIH utilizes the creativity and expertise of nutrition scientists throughout the country.

In FY 1988, for example, the NIH supported more than 25,000 extramural research grants and awards, including approximately 2,000 for nutrition research, to more than 1,200 institutions in every state of the Union and a number of foreign countries.

Three major funding mechanisms serve as administrative instruments for accomplishing NIH program goals through the efforts of scientists outside the NIH. The mechanisms are financial assistance awards (grants and cooperative agreements) and acquisition awards (contracts), as described in Appendix C.

Awards are made to extramural institutions following a carefully executed scientific review known as the peer review process. Studies within the NIH intramural research program are also subject to scientific review.

The research highlighted in this section does not provide a comprehensive list of the over 2,000 nutrition research and training projects funded in FY 1988, nor is it inclusive for each topic presented. Rather, for this issue of the annual report, we have chosen to include scientific topics that represent certain selected important topics: nutrition and AIDS; nutrition and human genome research; nutrition and behavior; and nutrition and disease prevention.

NUTRITION AND AIDS

Acquired immunodeficiency syndrome (AIDS), the epidemic disease of the latter 20th century, has created a public health emergency that will continue well beyond the year 2000.

Although AIDS is primarily characterized by immune dysfunction, weight loss and deteriorating nutritional status are critical factors in the disease process. Anorexia, nausea and vomiting, fever, and diarrhea are common features of advanced AIDS, as are malabsorption of fat, carbohydrate, and protein along with intestinal injury and malfunction. Consequently, severe malnutrition in advanced AIDS leads to abnormalities of specific components of the immune system and depletion of energy reserves needed to support cell growth. This has been called HIV wasting syndrome.

Although opportunistic infections, particularly from pneumonia and tuberculosis, most often cause death in AIDS patients, wasting is a hallmark of advanced disease, and may be closely correlated with approaching death. Prior to that stage, gastrointestinal manifestations can be unusually severe. The implications for studying nutritional therapies are enormous.

The underlying immune dysfunction associated with AIDS results in pathogen adherence to and penetration of intestinal mucosa, giving rise to chronic infections from viruses, fungi, parasites, and bacteria. The result is extensive tissue damage in the intestinal tract, leading to nutrient malabsorption, increased loss of protein and other nutrients from the intestine, and further systemic immune stimulation from antigens transiting the bowel wall. As part of this malnutrition, patients suffer deficits of essential micronutrients and nutritional substrates. As a result there is little energy to support normal immune responses and other body functions. The timing of death may be determined as much by the body's energy reserve as by the activity of the disease process itself. Malnutrition can impair the function of the immune system and affect the susceptibility of individuals to infection and thus contribute significantly to morbidity and mortality from AIDS.

Several NIH institutes are contributing to an understanding of the unique constellation of nutritional factors operative in AIDS. The following are a few examples of research that NIH-supported scientists are exploring:

Clinical and Animal Studies

Since malnutrition and wasting are major problems in the clinical management of AIDS, NIH-supported investigators are studying AIDS patients with diarrhea and weight loss to determine how the virus and the disease affect the gastrointestinal tract, to characterize the nutritional consequences of AIDS, and to develop new treatments.

- Since intestinal disease is a particular problem in infants and young children, investigators are studying the pathophysiology of intestinal dysfunction and the relationship to nutrient absorption. The gastrointestinal tract has a central role in growth and development and as a portal of entry for infectious pathogens. Possible factors contributing to malnutrition in HIV-infected infants and children include infections with bacterial, viral, or parasitic pathogens; chronic diarrhea due to intestinal colonization with aerobic and anaerobic bacteria; malabsorption of ingested nutrients due to acquired deficiencies in intestinal enzymes; as well as direct infection of the intestinal tract with HIV. Detailed nutritional and anthropometric data are being collected on perinatally infected infants and control children matched for age and socioeconomic status. Successful interventions for the prevention or treatment of intestinal dysfunction in AIDS could result in a significant reduction in the morbidity associated with HIV infections in children.
- In an effort to overcome weight loss, failure to thrive, and malnutrition in infants and children infected with HIV, researchers are investigating nutritional factors in AIDS, focusing both on nutritional status and requirements, gastrointestinal absorptive capacity, and immunohistochemical assessment of the intestinal mucosa. An associated study of simian immunodeficiency virus (SIV) on gastrointestinal function in juvenile macaque monkeys is allowing investigators to determine analogies between human and simian pathology.
- Several investigators have documented nutrient malabsorption and extensive histologic damage in the intestinal tract of AIDS patients, noting a striking lack of tissue repletion in the intestinal tract even during periods of apparent disease stability. This finding has resulted in an hypothesis that AIDS may progress through a self-perpetuating cycle of immune deficiency leading to intestinal damage, malabsorption, and malnutrition, which causes further immune deficiency. In order to clarify the clinical significance of this concept, researchers are studying nutritional rehabilitation, and the reestablishment in AIDS patients of the mucous membrane's functional barrier to the environment. An intestinal perfusion study is assessing salt and water absorption, intestinal permeability, and biliary and pancreatic function with a series of noninvasive tests to measure fat absorption, bile salt metabolism, bacterial overgrowth, pancreatic function, ileal secretions, and intestinal permeability.
- Approximately 250 patients with AIDS are being examined every 3 months over the entire clinical course of their disease. Medical scientists are determining nutritional status (weight, anthropometrics, body composition, dietary intake); gastrointestinal symptoms (dysphagia, nausea, vomiting, diarrhea, malabsorption); gastrointestinal infections; energy balance (energy expenditure and caloric intake); intercurrent health factors; and immune function. Observations from the study are being used to correlate changes in nutritional status with the frequency, severity, and outcome of individual infections and malignant complications arising in the AIDS patient population. In addition, all participants are receiving dietary counselling to meet any identified nutritional deficiences in terms of calories and macro- and micro-nutrients.
- Other investigators are studying a pig model of cryptosporidiosis by creating a T helper cell deficiency in these animals. Researchers are examining the impact of the organism on whole intestinal tissue, in human colonic epithelial cell cultures, and in porcine small intestine epithelial cells. They are comparing structural damage and the activation of inflammatory cells in both normal and immune-suppressed pigs to learn definitive information about diarrheal mechanisms, which may provide clues to possible immune control of the infection and improvement in nutritional status.

- Other animal studies in SIV-infected rhesus monkeys are also focusing on the pathophysiology of diarrhea--the most common characteristic of the simian disease. The affected monkeys are being evaluated microbiologically, clinically, pathologically, and nutritionally to determine the etiology of SIV-related diarrhea and the best methods of treating it.
- Sometimes diarrhea and weight loss in AIDS patients occur without the presence of a superimposed infectious agent. Certain characteristics of the disease suggest that the HIV virus may interact with a receptor on mucosal cells which leads to the release of peptide hormones, which, in turn, induce intestinal secretions (gastric inhibitory peptide, calcitonin, neurotensin, and bombesin). Investigators are developing a profile of these peptides prior to and during the course of diarrhea. By having a better understanding of which peptides are elevated during a particular disease phase, they hope to develop a more specific therapy for this debilitating nutritional problem.

Molecular Research in Nutrition and AIDS

Much NIH-supported medical research today is in a rapidly growing scientific field called molecular biology which is concerned with understanding the function and mechanism of action of biologically important molecules. If scientists understand the precise structure of the individual components of cells, they may be able to work with these elements to selectively control their activity. During the past year, NIH funded investigators have made rapid strides in analyzing the proteins, nucleic acids (DNA and RNA), carbohydrates, lipids, and other essential molecules that together constitute the human cell.

The following highlights represent a few of the NIH nutrition-related molecular biology studies in AIDS:

- Proteins, which are essential to all life processes, are molecules made up of a number of amino acids arranged in a specific order determined by genetic code. During the past year, investigators have determined the amino acid sequence of over 220 proteins and peptides by automated protein sequence analysis. Among the most important analyses have been those that have characterized and identified certain enzymes and other encoded gene products of HIV and those that have delineated the structure of T cell activating protein (TAP) and related lysine-6 encoded molecules.
- Vitamin D is essential to health, especially the absorption of calcium and phosphorus in the body. Sarcoidosis and lymphoma, both AIDS and non-AIDS-associated, are two relatively common diseases connected with the uncontrolled proliferation of lymphoid cells that can become much more serious when vitamin D metabolite-mediated hypercalcemia develops. In hypercalcemia, abnormally high levels of calcium appear in the blood. Several vitamin D hypercalcemia-causing metabolites are believed to be involved. NIH-funded scientists are trying to understand the mechanisms of these metabolites in order to develop inhibitory agents that can be safely used in treatment. In addition, they are exploring the role of retroviruses, including HIV, in modulating the expression of active vitamin D synthesis in human immune cells.
- Analogs of folate, a member of the vitamin B complex, and para-aminobenzoic acid (PABA), also a part of the vitamin B complex, are being investigated to identify compounds with therapeutic potential against opportunistic infections in AIDS patients. Analogs are chemical compounds with a structure similar to that of another, but differing in a certain component, which renders the compounds either similar or opposite metabolically. Folate analogs have been screened for inhibitory action against dihydrofolate reductase isolated from *Pneumocystis carinii*, which causes a highly virulent pneumonia in AIDS patients, and *Toxoplasma gondii*, the agent of a fulminating, highly infectious disease that can cause extensive damage to the brain, eyes, skeletal and cardiac muscles, liver, and lungs. One folate analog, methotrexate, has been clinically successful in treating AIDS patients with pneumonia due to *Pneumocystis carinii*.

NUTRITION AND HUMAN GENOME RESEARCH

Gene mapping, the process of determining the locations of genes on chromosomes, helps scientists understand inherited nutrition-related and other diseases, leading to new ways to diagnose, treat, and prevent such problems. To date, research has enabled scientists to either map or almost pinpoint the location of genes associated with such genetic diseases as Duchenne muscular dystrophy, cystic fibrosis, and hypercholesterolemia.

The 50,000 to 100,000 genes in the nucleus of each human cell direct the manufacture of thousands of proteins that the cell needs to perform its tasks. Usually, genes transmit their messages faultlessly. However, if a gene is flawed, a defective protein may result and cause disease.

Although many of the more than 4,000 presently known genetic diseases are rare when considered individually, together they cause intense and widespread suffering. The following example shows how two NIH-supported investigators discovered answers to a serious genetic disorder in which the cell produces too much cholesterol, greatly increasing the person's risk of heart disease and early death.

The two scientists discovered various defects in a specific type of receptor on the surface of some cells. Receptors are proteins that recognize specific chemicals from outside the cell and send appropriate chemical signals into the cell's interior. As a result of their research, they uncovered the relationship of the disorder hypercholesterolemia to low density lipoprotein (LDL) receptor genes--a discovery that has enabled them to begin to delineate the problem.

Cholesterol esters packaged in lipoproteins are delivered to the cells by means of lipoprotein receptors. Strategically located on the surface of the cells, the receptors on the cell surface bind to LDL, which carries cholesterol in the blood, and bring the cholesterol into the cell. The receptor also allows large amounts of cholesterol to be delivered to body tissues, avoiding the build up of atherosclerotic plaques on the artery walls, which occurs in hypercholesterolemia.

The LDL receptor was elucidated first from isolated human cells, although whole animal research is usually involved in uncovering metabolic pathways. Before new therapy could be designed for this genetic problem, the functions of the receptor in the body had to be determined by the investigators.

Understanding receptor binding has many implications in human nutrition. Heredity and diet seem to be major factors for the high levels of plasma LDL frequently found in Western societies which consume high fat diets. Diets rich in animal fats and cholesterol may elevate plasma LDL-cholesterol through the LDL receptor role of saturation and suppression. In understanding the role of diet in the treatment of elevated blood cholesterol levels, it is necessary to consider genetic variability among individuals. An important goal is to identify genes that determine the individual's susceptibility to contributory risk factors and to analyze the genes in appropriate cases.

As this example demonstrates, NIH supported research over the past decade has led to a tremendous number of advances in scientific techniques that are at the hub of a new effort to map and sequence the human genome--to determine the complete set of genes contained in the chromosomes of each cell of an individual. Such advances involve the ability to map genes and to sequence genetic material, namely deoxyribonucleic acid (DNA), the chemical essence of heredity.

These advances have allowed NIH to embark on the massive human genome project--a very complicated task that involves mapping the location of every human gene along the 46 chromosomes (23 pairs) in each cell. Each chromosome contains DNA. The genes are located along the thread-like chromosomes, strung almost like beads. Once identified, sequencing will determine the sequence and order of the chemical subunits of DNA in the segments of genetic material. This enormous targeted effort, which will take place over the next few years, is expected to have a profound effect upon future medical practice, possibly determining how to prevent or treat not only known genetic diseases, but also to lead to a much better understanding of such diseases as hypertension and cancer that have genetic components.

Most of the gene mapping and related research to date has involved separate studies in human genetics related to disease, much like the research directed at familial hypercholesterolemia. The scientists involved are usually searching for gene defects that play specific roles in disease.

A partial listing of NIH gene-related research projects, related to nutrition, follows:

- An investigator has cloned the gene responsible for phenylketonuria (PKU), a genetic disorder in which the absence of, or deficiency in, the enzyme necessary for the conversion of the amino acid phenylalanine into tyrosine causes the accumulation of phenylalanine and its metabolites in the body and urine. Symptoms include eczema, an unusual odor to the urine, and progressive mental retardation. Treatment includes a diet very low in, or free of, phenylalanine. Most states routinely test newborns for the defect. By sampling the outer membrane of the embryo sac, researchers can use the cloned gene to detect the disease very early in gestation.
- Lipid storage diseases are inherited conditions in which complex fats build up in tissues, causing mental retardation, enlarged spleen and liver, bone degeneration, and sometimes early death. In one of these disorders, Gaucher's disease, a deficiency of the enzyme glucocerebrosidase causes a lipid to accumulate with harmful effects in the liver, spleen, and bone marrow. After looking closely at the genetic material, the researcher developed a method of replenishing the enzyme by targeting intravenously injected glucocerebrosidase, purified from human placental tissue, to lipid-storing cells. Long-term improvement was observed in one patient treated by this method. If this approach proves clinically significant in a number of patients, it may serve as a model for the treatment of other enzyme-deficiency disorders.
- After carefully studying the biochemical mechanism of an inborn error of metabolism, NIH researchers discovered the genetic deficit responsible for the lethal heritable disease cystinosis. Because of the defective gene, cells do not manufacture a membrane transport protein that shuttles the amino acid cystine out of lysosomes--the specialized part, or organelle, of the cell which contains enzymes that function in digestive processes within the cell. Trapped within these organelles, cystine accumulates to toxic levels and eventually kills the cell. The toxic accumulation of cystine in the affected child retards growth and produces kidney damage severe enough to require transplantation. Researchers discovered that in patients treated with cysteamine, a substance chemically related to cystine, the compound would deplete cystine by reacting with it to form products that escape from the lysosome via pathways not requiring the transport protein. Young patients receiving oral cysteamine appear to be growing normally, with their kidney function stabilized.
- Patients with hereditary hemochromatosis absorb excess iron from the intestines resulting in the deposition of iron in a number of tissues. NIH-supported investigators are attempting to isolate and characterize the gene responsible for this disease. Previously, the hemochromatosis gene had been mapped to a portion of the human leukocyte antigen (HLA) locus on chromosome six. Further studies will try to characterize this gene, and then to use a DNA probe, a single sequence of single-stranded DNA that is complementary to the DNA sequence being sought. It will be used to detect the mutation, which recognizes it, in other single strands. The probe is usually made radioactive so that it can be detected. In addition, ribonucleic acid from ferritin, a molecule from the intestinal tissue suspected of causing the defect, will be analyzed.
- Recombinant DNA techniques in combination with the use of DNA restriction enzymes and nucleic acid hybridization are being used to establish genetic DNA markers for the diagnosis of many hereditary diseases. Researchers are employing these techniques to study genetic diseases for which the basic defect may not be known such as multiple endocrine neoplasia (MEN-2A). DNA restriction enzymes are used to break up the DNA of affected individuals into sets of fragments which can be resolved into bands by gel electrophoresis. Since these enzymes cut the DNA at specific base sequences, the fragments resulting from particular chromosomes will always resolve into the same banding pattern if the base sequences are the same. If there is a deletion, insertion, or mutation somewhere, however, the band containing it will migrate differently from the normal band and a new pattern will appear. These

patterns are restriction-fragment-length polymorphisms (RFLP) and they can be used to trace the inheritance of particular chromosomes through a pedigree. If the defective gene has been isolated and a recombinant DNA probe exists for the particular sequence, nucleic acid hybridization can be used to identify the exact chromosome fragment containing the gene. If affected members within a family can be shown to inherit the particular genetic disease only when they carry a particular chromosome identified by an RFLP and/or DNA probe, then it is likely that the gene for that disease resides on that chromosome. Carriers can also be detected in this way. The RFLP technique has been used successfully with cystic fibrosis to identify which chromosomes carry the involved genes and to identify carriers and affected individuals in some families, even though the exact nature of the biochemical defect is not yet known.

- An investigator and his team of researchers have determined the amino acid sequence of the gene that codes for osteonectin, a protein that is critical for proper bone structure and function. The researchers have developed an antibody that specifically recognizes osteonectin, which will allow them to further elucidate the molecule's function.
- Gene transfer, a powerful new technology in which genetically altered cells are inserted into human beings, has potential use in the treatment of cancer, AIDS, and a variety of genetic diseases such as adenosine deaminase (ADA) deficiency, thalassemia, PKU, and sickle cell anemia. For gene therapy to be successful, the gene must not only be taken up by the cell, it must also be expressed; that is, the cell must make the protein product specified by the DNA and make it in quantities sufficient to correct the defect involved in the genetic disease. So far, transferred genes have mostly been expressed poorly, if at all. However, progress is being made toward a better understanding of the mechanism for gene transfer. For instance, scientists are learning more about ways to target genes to specific sites within the cell's DNA. Since inserted DNA often integrates in a random fashion, researchers think that if new DNA can be targeted into the site where it is normally found, it should be expressed better. NIH-supported scientists are at the forefront of this gene targeting research. They have shown that by using a mechanism called homologous recombination, they can target correct DNA sequence to a specific defective gene in cultured cells. Although the new DNA corrects the gene, investigators must do much more research before the technique is refined enough for gene therapy. When finally developed, gene transfer will have direct implications in nutritionally related genetic diseases such as PKU.

NUTRITION AND BEHAVIOR

A dynamic overlap exists between the disciplines of behavior and nutrition. Behavior is one of several significant factors that determine food choice and often changes in diet patterns necessarily involve changes in behavior. Eating itself is a behavior controlled by the brain and disorders of eating inherently involve the central nervous system.

The development of effective means to reduce the nutrition related factors associated in part with chronic disease is a major public health goal, according to *The Surgeon General's Report on Nutrition and Health*. The publication notes: "... improvement of food choices and dietary practices of individuals and populations is the key to the control of conditions reviewed in this Report."

The problems associated with dieting and obesity in the United States are numerous and offer many behaviorally related paradoxes. For example, many cultural factors in the U.S., including television and associated advertising, promote food intake, inactivity, and leanness--values which are almost impossible to reconcile. Obesity, according to "The Surgeon General's Report," is a common problem in America today, affecting about 34 million people. The results of the 1985 National Health Interview Survey showed that 46 percent of the women and 26 percent of the men were on a diet. Sixteen percent of the females were always on a diet. Consequently, the search for the "ideal" American body shape and weight is associated with many complex cultural, health, and behavioral aspects.

NIH-funded investigators are trying to bring greater understanding to the many unresolved, sometimes paradoxical questions involving nutrition and behavior. With the help of technology developed over the last decade, these efforts also include research on nutrition-related effects on brain function. The following highlights represent a few studies in these areas:

Obesity

- Researchers are investigating patterns of eating in lean and obese human subjects in their natural environments to discover differences between the two groups. They are studying eating behavior as it relates to the microstructure of meals as well as the total 24-hour eating patterns connected with food and nutrients. In measuring microstructure of meals, they are determining the patterns of chewing and swallowing to reveal the initial rate of eating and changes in rate duration, and total amount of eating prior to satiation. In studying 24-hour eating patterns, they are looking at the duration, size, and frequency of both meals and snack times. They are recording all chews, swallows, and drinking with an oral sensor. Eating patterns are being telemetered to a 24-hour tape recorder worn on the belt. The investigators are attempting to behaviorally classify the obesities, to develop specific recommendations for the behavioral control of eating, to monitor compliance with diet programs, and to develop an approach to continuously monitor and signal patients when they eat too fast, too long, or too often.
- An obesity behavioral treatment approach has been adapted for a small lightweight portable computer and is being tested against therapist-conducted treatment in 342 women who are 20 to 40 percent overweight. The women have been divided into three groups: a therapist-conducted weight reduction program (12 sessions over 20 weeks); computer-assisted therapy with group support (5 sessions over 20 weeks); and unsupported computer-assisted therapy (1 introductory session only). Half of each computer assisted group is receiving the computer for 12 weeks and half for 20 weeks. The major expected outcome is weight change. The women are reporting their own eating behavior and activity levels, being asked about selected psychological factors, and about the acceptability of the treatment approaches. From the data, investigators will not only compare weight loss between groups, but also behavior changes induced by computer-assisted or therapist-conducted treatment. Investigators are taking the frequently collected caloric consumption and activity data to develop a model of weight loss.

Anorexia/bulimia

- Adolescent females often "diet" by drastically reducing their food intake, or by inducing vomiting. Sometimes these unhealthly practices are associated with low self-esteem, substance abuse, poor body image, or depression. However, the problems associated with unhealthy weight regulation practices in adolescent females need to be carefully delineated in order to develop appropriate preventive strategies. All 6th and 7th grade females, ages 11 to 13, in 6 middle schools are being assessed yearly by NIH-supported investigators over a 3-year period, using a variety of techniques. Height, weight, skinfold thickness, serum cholesterol, and somatomedin C are being measured. The girls reported their knowledge of and attitudes toward weight reduction, gave their own assessment of their weight regulation behaviors, indicated their activity per week, and their frequency of eating over the past month. Average daily calories, saturated fat, cholesterol, protein, and carbohydrate intake are being calculated from the food frequency information. The researchers are looking at psychological data, including the Eating Disorder Inventory (EDI), and measures of body image, depression, anxiety, self esteem, and family attitudes and values. Every three months over the 3-year study period, the students are being assessed for weight, height, pubertal development, the EDI, and weight regulation behaviors. The relative risk factors developed in the study will serve as a basis for preventive interventions associated with problem dieting in adolescent females.

Cancer

- Anorexia is a very common problem in cancer treatment that limits aggressive therapy for the disease, worsens the patient's condition, and contributes to mortality rates. Many hypotheses for cancer anorexia have been advanced, but no complete answer has been discovered.

NIH-supported scientists are working on this problem from several different perspectives. In one study of 300 cancer patients, learned food aversions appear to form following the pairing of food with the sickness that follows certain types of treatment. In an effort to stop these adverse treatment side effects, researchers are characterizing learned food aversions associated with radiotherapy, assessing the role of nausea and vomiting as an inducing agent in this phenomena, and assessing the efficacy of different potential blocking agents that may protect foods in the patient's diet from becoming aversive. The patients are being evaluated before their first course of therapy and at designated time points over the following six months. Their acquisition of food aversions are being ascertained with open-ended questionnaires on food items consumed in close proximity to treatment. Patient nutritional status is being monitored by assessments of weight; serum albumin; transferrin, a globulin that binds and transports iron; and total lymphocyte count. The role of the emetic reflex in the acquisition of learned food aversions will be determined by monitoring an antidiuretic hormone in patients who either do or do not form aversions. By learning more about the nature and clinical implications of learned food aversions in cancer patients, scientists hope to exert a positive impact on the quality of their lives, improve disease prognosis, and avoid anorexia.

- In another study, the results of research with experimental cancers in animal models suggest that large quantities of glucose and amino acids are removed from the circulating blood by the tumor mass. The major products of tumor metabolism appear to be lactic acid and ammonia. Recent studies have demonstrated a threefold elevation in blood ammonia in anoretic tumor-bearing rats and a tenfold increase in ammonia concentration in blood draining the tumor mass. Ammonia intoxication produces anorexia and elevations of certain neurochemicals in the brain. Researchers have hypothesized that increased ammonia concentrations in the blood and brain and the neurochemical aberrations induced by the detoxification of ammonia in the brain are very important factors in the development of cancer anorexia. They are now testing that hypothesis by determining the relationship between alterations in blood and brain ammonia on the onset of anorexia in tumor-bearing rats and by assessing the effects of ammonia infusion on food intake and neurochemistry in normal rats.

Cardiovascular disease

- The effectiveness of family-based health behavioral change is being tested in Anglo and Hispanic-American families of fifth- and sixth-grade elementary school children. The study is assisting family members in initiating and maintaining dietary and other changes linked to risk factors for cardiovascular disease. The family is the major environment in which health behaviors are developed. In addition to selected physiologic measures, direct observation of behavior, family process, acculturation, social support, and self-efficacy are being used to study the mechanism of health behavior changes in families and to detect the ethnic differences in these processes.
- Longitudinal studies begun on 3- and 4-year-old children and their families are being conducted by several investigators from different research institutions throughout the U.S. to discover the early behavioral roots associated with dietary and other risk factors for cardiovascular disease. The results of these studies should provide information on the educational, ethnic, social, taste preferences, television, temporal, and other enviornmental influences on diet and activity.

Neuroendocrine Research

Many new technologies assist investigators in studying the central nervous system, and its relationship to nutrition and behavior. Scientists have been involved in many breakthroughs related to identifying new neurotransmitters, the chemicals that affect or modify the transmission of impulses across the synapse, the tiny gap between two neurons or between a neuron and a muscle. Methods for labeling neurotransmitters have led to their use in radioactive scanning. With positron emission tomography (PET), the normal location of these transmitters as well as any abnormalities produced by disease can easily be revealed in the living brain. PET scanning with fluorodeoxyglucose reveals the metabolic activity of any area in the brain during any task and in any disease.

Nutrients are involved in most hormone activity and in enzyme systems associated with various metabolic pathways. Alterations in nutrition can change the availability of neurotransmitter precursors so that neurotransmitters change their concentration and ultimate activity. Basic research into nutrition is vital to discovering the multiple relationships between metabolic pathways in the body and those in the brain. The appreciation by NIH researchers of the importance of receptors for hormones and neurotransmitters has led to the isolation and chemical characterization of many of these important biological entities. Consequently, scientists are learning how hormones and neurotransmitters quickly trigger changes in cellular activity.

As a result of the many technological breakthroughs, investigators are studying the development and functional organization of the nervous system, with specific focus on molecular mechanisms. Nutrition scientists are utilizing a number of related disciplines, including physiology, biochemistry, biophysics, morphology, immunology, and molecular biology. They study neuropeptides and other neurotransmitters, neuropeptide receptors, plasma membrane and intracellular membrane systems, cytoskeletal proteins, and various enzymes which are found in the nervous system, are essential to its function, and often are associated with behavior.

The following research highlights represent a few of the basic studies in this field:

- A number of peptides, short strings of amino acids joined together, are being measured in spiking and nonspiking tissue from epileptic patients. Neuropeptide Y and somatostatin, an inhibiting peptide, are elevated in these tissues. Somatostatin is involved in many metabolic pathways throughout the body. Somatostatin elevation has been noted by a number of investigators in the rat model of epilepsy. The correlations between these peptides and seizures are still unclear.
- Researchers are studying the role and chemical composition of fibrous elements within normal and abnormal brain cells. Their work has also focused on neurofilaments--elements within the cell that are made up of long hair-like strands of protein--and on the development of neurofibrillary tangles in Alzheimer disease. They found that the proteins in Alzheimer tissue are highly resistant to standard protein solvents, which means they do not readily dissolve and disappear. In fact, they may actually create a physical barrier that blocks the normal transport of nutrients within nerve cells. At first, the scientists thought that the protein molecules were binding tightly together to form an extremely rigid "cross-linking" structure. Their latest thinking is that the proteins have a pleated structure that accounts for their rigidity.
- This same scientific group developed an antibody that can selectively label certain helical filaments in the brain of Alzheimer patients, clearly distinguishing them from normal brains. As the investigators continue their work toward full characterization of neurofibrillary tangles, they have started looking for related proteins in cerebrospinal fluid and blood samples, with the idea of developing a simple means of diagnosing Alzheimer disease.
- Researchers are investigating cellular mechanisms of myelin breakdown, with emphasis on those related to multiple sclerosis and other demyelinating diseases. Myelin is the complex material containing phospholipids and proteins that forms a sheath around the axons of certain nerve fibres. They continue to look for what causes these abnormal breakdowns in cellular material.
- A researcher is investigating several nutritionally related behavioral/biochemical correlates related to Parkinson's disease, a common illness of aging that affects 1.5 million persons in North America. In addition to the motor manifestations associated with this condition, victims frequently suffer from depression. This investigator is studying a reduction in brain serotonin which, as a neurotransmitter, has been implicated in the depression. The scientist will also study the precursor of serotonin, 1-5-hydroxytryptophane, derived from an essential amino acid. He will determine its role in the aging nervous system.

NUTRITION AND DISEASE PREVENTION

The Surgeon General's Report on Nutrition and Health, published in 1988, noted that dietary factors are associated with 5 of the 10 leading causes of death for Americans. These illnesses include coronary heart disease, stroke, atherosclerosis, diabetes, and some types of cancer. Altogether these account for two-thirds of all deaths in the United States.

"The Surgeon General's Report" said that for most Americans overeating--too many calories and an imbalance in nutrients--was a major health concern. The report noted that although much was still uncertain about how dietary patterns protect or injure human health, enough had been learned about prevalent dietary patterns in the U.S. to recommend prudent changes.

In fact, the report's main conclusion was that "overconsumption of certain dietary components is now a major concern for Americans. While many food factors are involved, chief among them is the disproportionate consumption of foods high in fats, often at the expense of foods high in complex carbohydrates and fiber that may be more conducive to health."

Last year, in the *11th Annual Report of the National Institutes of Health Program in Biomedical and Behavioral Nutrition Research and Training*, this chapter presented research highlights on "Nutrition and Heart Disease," "Nutrition and Cancer," and "Nutrition and Obesity," emphasizing two of the nation's most important "killer diseases," plus a third related high risk factor.

Despite a recent sharp decline in death rate, coronary heart disease is still the number one cause of mortality. Cancer is the second leading cause of death from illness in the U.S., according to the Surgeon General. Obesity affects over 34 million Americans, ages 20 to 74, with the highest rates in poor and minority groups.

This year, section 3 will cover disease prevention in three more major illnesses in which, according to "The Surgeon General's Report," dietary excesses or imbalances exacerbate or contribute to the disease: stroke, diabetes, and osteoporosis.

The term "disease prevention" denotes one phase in the biomedical research process. After a disease is identified, research takes many different directions. For example, investigators may begin epidemiologic studies to identify incidence and causal relationships. Basic research protocols are started to discover mechanisms and possible metabolic pathways. Cellular and molecular research tries to determine biophysical alterations and begins the long process of developing alternatives. Animal investigations then test the alternatives. If these are successful, clinical trials next try to prove the value of new drugs, practices, or procedures on human patients. If these studies are successful, adoption by the medical community should follow. Finally, education and demonstration projects take the information to the public, testing the value of preventive techniques in relationship to risk factors. Naturally, not all facets of this process are applicable to every disease, nor do they necessarily always follow the same pattern. Research is not a stepwise process; it proceeds in multiple directions at once.

Stroke

Stroke occurs in about 500,000 persons per year in the United States. In 1987, 150,000 deaths were recorded with long-term disability in many more individuals. Approximately 2 million living Americans suffer from stroke-related disabilities, at an estimated annual cost of more than $11 billion.

Unlike other organs of the body, the brain cannot store energy. It depends on a continuous supply of fresh blood pumped to it by the heart. About 25 percent of the blood from the heart goes to the brain. If blood flow to a section of the brain stops for any reason, brain cells in the area lose their source of energy and begin to die, which is called stroke.

Stroke is the result of sudden loss of brain function from one of four major vascular events: thrombosis, or blood clot, in a cerebral artery; embolism, or blockage, of a cerebral artery by a circulating clot; stenosis, or narrowing, of a cerebral artery by atherosclerosis; or hemorrhage from rupture of a cerebral artery.

The major risk factors for stroke are in part related to dietary factors. Hypertension, atherosclerosis, heart disease, diabetes, and obesity are predisposing factors to stroke. The process of disease prevention is interrelated. Current evidence suggests that certain dietary factors that promote high blood pressure, including obesity, sodium, and alcohol, may increase the likelihood of stroke.

Persons with hypertension are at greatly increased risk for stroke. This risk increases with elevation in blood pressure regardless of age and sex; it decreases when blood pressure is reduced. How hypertension predisposes to stroke is not fully understood, but the disease appears to injure the cerebral artery walls. The link between diet, blood cholesterol levels, and stroke is not clear.

The following are NIH-supported research highlights related to disease prevention and stroke:

- When investigators used a case control approach to study data from 2,000 individuals, the primary risk factors for stroke became clear. Diseases related to diet such as hypertension, diabetes mellitus, and definite hypertensive heart disease were important risk factors. Absolute risk of stroke was calculated as a function of the presence or absence of specific forms of cardiovascular disease.
- When disease prevention programs are aimed at adults, long-term injurious habits such as the wrong diet, inactivity, and smoking may be difficult to break. As mentioned previously, researchers have recognized that helping children develop good lifestyle habits while they are young is an excellent way to help them stay healthy. However, children must be reached within their primary environments--family or school. A longitudinal study of risk factors including physiologic (systolic and diastolic blood pressure, heart rate, serum lipids, and lipoprotein levels), behavioral (Type A behavior and its components), and lifestyle factors (diet, activity, and smoking) has been launched. Out of 120 families, researchers are studying two panels in this 4-year research project. The panels consist of 6- to 11-year-old twins and their parents. The interrelationships among risk factors, the extent to which they are due to environmental as opposed to genetic factors, and their stability over time are being investigated. Changes in lifestyle associated with development are being taken into account.
- Scientists are investigating risk factors for coronary heart disease and stroke in an older population, ages 65 to 84. Since atherosclerosis is prevalent in the elderly, the study is focusing on factors thought to induce clinically overt disease. Researchers will try to assess how to predict clinical disease based on preclinical conditions. Since cardiovascular events may occur in older persons as a result of health or life circumstances, participants are being evaluated at regular intervals to check diet, concurrent disease, social support networks, stressful life situations, physical activity, and other risk factors.
- Investigators are operating a Stroke Clinical Research Center to emphasize therapies focused on prevention, acute medical treatment, and rehabilitation techniques for cortical impairment. Among clinical studies, the preventive therapies are designed to assess various risk and prognostic factors in stroke patients. They want to develop a better understanding, at the molecular level, of both acute therapy and prevention. Among the risk factors being studied are cell cholesterol hydrolase activity, glycosylated hemoglobin, cholesterol turnover in plaques, and physiochemical bases for platelet behavior. In certain patients, researchers are studying compensatory learning strategies for neuropsychological and language impairment.
- High potassium diets reduce deaths from stroke in hypertensive rats by 90 percent. This protective effect is independent of lowering blood pressure. Apparently, high potassium diets allow cerebral arteries in the rat to carry higher pressure without sustaining wall lesions. High potassium diets also greatly reduce the incidence of cerebral hemorrhage and infarctions in hypertensive rats. The investigators are now studying hypertensive, hypercholesterolemic rabbits to determine whether a high potassium diet will reduce the deposition of cholesterol esters on the walls of the aorta and the carotid, vertebral, and coronary arteries. In another study, they are investigating whether magnesium, which along with potassium was four times higher in prehistoric man's diet, will protect hypertensive rats against stroke death, when given alone. In a third study, they will try to assess whether potassium protects against stroke deaths after lesions have started in hypertensive rats.
- As the taste system develops in mammals, there are taste changes in salt preference. The mechanisms of salt appetite are being studied in several fetal and young animal

models. Neurophysiological and neuroanatomical studies of the development of salt taste sensation demonstrate that these responses are accompanied by neural rearrangements. The number of fungiform papillae and taste bud receptive fields on the anterior tongue are altered. Another investigator in studying the preweaning taste exposure to salt and relating the saline intake to a relative insensitivity of the taste system. The experiments on salt taste sensation and how salt taste develops can contribute to understanding changing salt preference and the importance of prevention of excess salt intake in infants and children. High salt intake in human has been implicated in the development and maintance of hypertension which can be a factor in stroke.

Diabetes Mellitus

Approximately 11 million Americans have diabetes, almost half of whom have not been diagnosed. In 1987, the disease caused about 38,000 deaths, and contributed to an estimated 95,000 deaths from associated cardiovascular and kidney complications. In 1985, diabetes was estimated to cost $13.8 billion per year, or about 3.6 percent of the total health expenses in the U.S.

Diabetes is a complex and chronic metabolic disorder, which has as its most evident characteristic an elevated concentration of glucose in the blood. It results from either partial or total lack of insulin secretion from the pancreas, or to the inability of the insulin to function normally in the body. Long-term complications can involve multiple organs, including the eyes, kidneys, nerves, and blood vessels.

There are two common types of diabetes. Type I, or insulin-dependent diabetes mellitus, formerly known as juvenile-onset diabetes, accounts for about 10 percent of the disease in the U.S. It is characterized by an absolute lack of insulin, caused by destruction of the islets of the Langerhans in the pancreas. Type I diabetes usually appears before age 40 and has an acute onset. Affected persons often have normal body weight. Because of low insulin levels, Type I diabetics require insulin for survival. Treatment calls for insulin injections, diet coordinated with insulin dosage schedule, and regular physical exercise.

Type II diabetes, or noninsulin dependent diabetes mellitus, also known as adult-onset diabetes, accounts for 90 percent of the U.S. cases and affects at least 10 million Americans. It often appears in midlife, most commonly with people who are overweight or obese. Its onset is gradual, and many persons have a history of mild symptoms or no symptoms at all.

Mortality rates for white males and white females with Type I diabetes, or insulin dependent diabetes, are 5 to 11 times greater than those for the general population. The prevalence for Type II diabetes, noninsulin dependent type, is 33 percent higher in blacks than in whites, and mortality rates for blacks with this condition are twice that of whites.

The role of diet in diabetes treatment is major. At least 80 percent of those with Type II diabetes are 15 percent or more over their desirable body weight at the time of diagnosis. Certain experts suggest that new cases of this condition could be reduced by half by preventing obesity in middle-age adults. Also, significant calorie reduction seems to lower blood glucose levels even before weight loss occurs. When desirable weight is achieved, control of blood sugar can be accomplished by consuming just enough food to maintain correct weight. As the person reduces poundage to desirable levels, improvements in cardiovascular risk factors--hypertension and high blood lipid levels--also occur.

Lifelong care is required to reduce the risk factors and complications of Types I and II diabetes. The American Diabetes Association Task Force in 1987 noted that diet therapy was considered the key to diabetes management because of its role in controlling hyperglycemia in the most prevalent type of disease, noninsulin dependent diabetes. They said that the strategies used were similar to those designed to reduce excess blood lipid levels, blood pressure, body weight, and their associated cardiovascular risks in heart disease. They recommended maintaining blood glucose as close to physiologic levels as possible to prevent hyperglycemia and consequent damage to bodily systems in both types of diabetes.

There are many questions that surround disease prevention in diabetes, nutritional and other treatment approaches, and associated risk factors. A few examples of NIH-supported studies in these areas follow:

- For some time physicians have know that about 25 percent of adults with impaired glucose tolerance (IGT), a midly abnormal rise in blood sugar levels, go on to develop severe glucose intolerance in the form of noninsulin dependent diabetes (Type II diabetes). The question that has puzzled investigators about impaired glucose tolerance was whether it was due to a failure of the pancreas to produce insulin, the hormone that regulates glucose metabolism. Investigators now have shown that overweight adults with IGT have normal functioning pancreas glands able to produce high levels of insulin. Even when exposed to large amounts of insulin, however, their body tissues do not efficiently use blood sugar, a condition which is known as "insulin resistance." Consequently, insulin resistance, not insulin deficiency, is the abnormality underlying IGT. The investigators found that often weight loss alone could improve insulin's effectiveness. Moderate levels of glucose in the blood signal the pancreas to secret more insulin; however, it is likely that continued high levels of glucose will damage beta cells, the insulin-producing cells of the pancreas. Therefore, it is better to treat IGT with weight loss that to treat diabetes once it develops. They arrived at their conclusions after studying insulin action and secretion before and after development of impaired glucose tolerance in a group of 24 adults and in 254 other adults with the whole range of glucose tolerance, including frank diabetes.

- In addition to both Type I (insulin-dependent) and Type II (noninsulin dependent) diabetes, gestational diabetes (impaired glucose tolerance during pregnancy) occurs in 2 to 5 percent of all pregnancies, placing both mother and baby at special risk. In approximately 98 percent of the cases, the condition is transient, and the mother's blood sugar levels return to normal after the baby is born. A researcher is studying 400 black women with gestational diabetes to determine whether obesity, body fat distribution, fetal outcome, hypertension, thyroid disorders, family history of diabetes and/or heart disease, the presence of certain autoantibodies, and selected genetic and environmental factors are risk factors for gestational diabetic women to develop overt diabetes. An assessment is being made with a health hazard appraisal instrument as to whether lifestyle, socioeconomic status, dietary habits, and personality traits are related to the development of overt diabetes. Also, the women will be assessed yearly, in the future, for serum cholesterol, triglycerides, high density lipoprotein, low density lipoprotein, and certain other physiologic variables as predictors of overt diabetes or other diseases such as thyroid disorders and cardiovascular disease.
- Approximately 1,400 Type I, insulin-dependent diabetic patients, 13 to 40 years old, are being studied at 29 medical centers throughout the United States. This 6-year research project is designed to answer the important question: Will normalizing blood glucose levels help to prevent or ameliorate diabetic complications? It is the largest prospective, randomized study of this question ever undertaken, and the project is called the Diabetes Control and Complications Trial (DCCT). The DCCT is comparing "standard" and "intensive" treatment of diabetes. The standard treatment includes one or two injections of insulin daily, regular self-testing of urine or blood for glucose, and a routine clinic visit every three months. The intensive treatment includes insulin by injection three or four times daily or given continuously by insulin pump, frequent self-monitoring of blood glucose, an initial hospital stay, and clinic visits once per month. The intensive treatment is designed to bring blood glucose as close to nondiabetic levels as possible. The researchers will study blood vessels that line the back of the eye because they reflect the health of small vessels throughout the body. Changes in these blood vessels will be the primary measure of whether intensive treatment will help prevent complications. This approach means that the patients without diabetic retinopathy are being studied to determine whether the development of retinopathy can be prevented and those beginning the study with normal, nonproliferative retinopathy are being studied to determine whether established lesions can be improved or their progress halted.

Both types of treatments have the same dietary approaches as part of their regimen. Each patient is receiving an individualized meal plan that provides for the person's total nutritional needs. The meal plan is quantitative in nature, and is designed to be compatible with the person's insulin schedule and activity or exercise patterns. The plan is based on the American Diabetes Association's exchange lists, and is modified for a prudent fat diet. The meal plan is designed to promote normal growth and development in adolescents and to maintain ideal weight in adults. A dietitian at each DCCT site explains the meal plan initially and goes over the diet plan every 6 months with each patient.

Osteoporosis

Approximately 15 to 20 million Americans are affected by osteoporosis, which contributes to some 1.3 million bone fractures per year in persons 45 years or older. One-third of the women 65 years and older have vertebral fractures. On the basis of x-ray evidence, by age 90, one-third of the women and one-sixth of the men will have suffered hip fractures, leading to death in 12 to 20 percent and to long-term nursing care for many who survive. In 1987, the estimated total cost to the U.S. economy for osteoporosis and associated fractures was $10 billion, including direct expenditures (hospitals and nursing homes) and indirect expenditures (lost earnings).

Osteoporosis, literally meaning "porous bone," is a condition characterized by excessive loss of bone tissue and an increased susceptibility to fractures of the hip, spine, and wrist. As a result, bones become fragile and fracture easily, sometimes as the result of a gentle twist, slight pressure, or other seemingly normal movement.

As a skeletal disease in which nutrition plays a role, osteoporosis can be classified in primary and secondary forms. Primary osteoporosis can be further classified into postmenopausal osteoporosis (accelerated decrease in bone mass that occurs when estrogen levels decline after menopause) and age-related osteoporosis (the incremental loss of bone mass with age that occurs in men and women). Secondary osteoporosis may develop at any age as a consequence of endocrinologic and gastrointestinal conditions, or metabolic disorders, as well as prolonged bedrest which results in bone demineralization.

Since women have approximately 10 to 25 percent less total bone mass than men at maturity, they are more likely to develop osteoporosis. But it does not attack all women equally. Certain factors beyond the control of the individual put certain women at higher risk. These factors include being white (Caucasian and Asian women over age 60 are twice as likely as black women to have osteoporosis); early menopause, before age 45 (either naturally or surgically); being older; being thinner or small boned; and family history of osteoporosis. Several other lifestyle factors within the control of the individual are believed to predispose to osteoporosis. They are a chronic low intake of calcium and low physical activity level.

Although much is yet to be learned about how diet and lifestyle can affect the development of this disease, sufficient scientific evidence now exists to make nutrition-related factors a focus of programs to prevent or treat osteoporosis. The following studies represent some of the NIH-supported disease prevention research in these areas:

- Spinal osteoporosis is a very crippling disease that commonly afflicts elderly postmenopausal women. Approximately 5 million Americans suffer from spinal osteoporosis, with gradual loss of bone in the spine that results in crush fractures of the vertebrae. It is estimated that one-third of women over 65 years of age have spinal osteoporosis. The resulting shortened stature, curvature of the back, and abdominal protuberance cause much back pain and gastrointestinal discomfort. Treatments such as estrogen and calcium are directed at preventing bone loss before it occurs. However, these medical approaches have limited value in patients with established osteoporosis, in which substantial bone loss has already occurred. Many studies have shown that fluoride can stimulate bone formation. Long-term treatment with fluoride has been demonstrated to increase the mass of trabecular bone--a type of bone found in the spine. Unfortunately, sodium fluoride has caused side effects in users. By reacting with gastric acid, it can cause corrosion of the stomach lining and bleeding. It can also cause joint pain, tenderness, swelling, and sometimes more serious microfractures. It has even been suggested that its use is associated with hip fractures. Certain complications have been attributed to the formation of abnormal bone with mechanical properties that are not as good as normal bone. These many complications have precluded the widespread acceptance or use of fluoride in the U.S. NIH-supported investigators have tested a special slow-release formulation of sodium fluoride. By bypassing the stomach before a substantial amount of fluoride is released, gastrointestinal side effects are minimized. By allowing fluoride to be absorbed slowly, fluoride levels in the blood are also kept to an effective but not toxic level. Added to the slow-release fluoride in this study was a calcium supplement, calcium citrate, which permits newly formed bone to be adequately mineralized. Researchers followed a total of 251 patients using the sodium fluoride with calcium citrate treatment for at least 1 year, with the average study length being 3-1/2 years. In the patients, gastrointestinal complications were minor and occurred in 3.2 percent of patients. None had evidence of bleeding and only 1.6 percent had joint pain. Documented stress fractures were encountered in only two of 251 patients. Bone density of lumbar spine increased or stabilized, with an increase per year of 3 to 6 percent in bone mass for up to 4 years of the study. Additional studies may be required to accurately determine the fracture efficacy of the slow release sodium fluride treatment.

- A 20-year research project has been under way for the past 6 years to study 199 normal women, ages 35 to 45 at the study's start, prior to the onset of osteoporosis, to learn much more about numerous variables associated with disease development. The objectives of the research are: to obtain comprehensive longitudinal data on calcium metabolism, bone metabolism, and related physiologic functions in a group of untreated women from the perimenopausal period to the median onset time of osteoporotic symptoms; to provide a physiologic profile both of the women who develop symptomatic osteoporosis, and those who do not, allowing characterization of the differences and of the factors that influence those differences; to permit better identification of the osteoporosis-prone subset in order to provide a rational basis for prophylactic treatment, and better identification of high risk persons; and to characterize the interrelationships between major physiologic variables during a key time in osteoporosis development.
- Two hundred healthy women between 20 and 25 have been recruited from students at several university professional schools to test the hypothesis of NIH-supported investigators that calcium intake measurably influences the peak adult bone mass achieved after cessation of growth. The effect of other nutrients such as protein, phosphorous, alcohol, and caffeine on this consolidation of bone mass is also being tested, in conjunction with self-chosen levels of physical activity. Researchers are making dietary evaluations at 3-month intervals throughout the study and bone-mass measurements at 6-month intervals. Physical activity is being measured at 6-month intervals using an activity meter worn on the wrist for a 7-day period. The researchers are hoping to confirm findings of other studies of increased bone mass occurring after cessation of linear growth and to define the determinants of this increased mass. They hope to show that peak skeletal mass is influenced by nongenetic factors and is amenable to intervention early in life, in order to give women greater skeletal mass prior to the start of age-related bone loss at about 40.
- Researchers are trying to determine whether a program of aerobic exercise in combination with calcium supplementation can enhance bone mass in a young premenopausal population. The scientific literature contains little information on exercise and calcium in relationship to skeletal health. The 120 subjects are being placed in one of four groups: exercise, exercise plus calcium, calcium, and control. The women in the exercise group will visit the gym three times per week. Assessment of bone mineral, fitness, and endocrine status were performed at the start of the study and at 8-month intervals thereafter. Researchers expect to find differential skeletal response to the prescribed regimens, as compared to the control group. The results should offer a basis for developing future interventions

aimed at increasing peak bone mass and improving skeletal health.

- Studies are under way to define the interactions that occur between lead and calcium at the level of the intestinal cell and how they affect intestinal transport.

The biological interactions between lead and calcium are complex; little is known regarding their cellular and molecular absorption represents the first critical step in maintaining systemic and cellular calcium homeostasis.

Section 4. Biomedical Research and Training in Nutrition

NIH BIOMEDICAL RESEARCH AND TRAINING IN NUTRITION -- THE LEADER IN FEDERALLY SUPPORTED NUTRITION RESEARCH AND TRAINING

The Current Picture

In FY 1988, the NIH led all Federal agencies in financial support of nutrition research and training, for an unprecedented total of $276.2 million. This figure represents the combined individual contributions of the 12 NIH institutes, 2 centers, and 1 division that support biomedical nutrition research and training. Table 4 shows actual obligations for FY 1988 biomedical nutrition research and training for all NIH BIDs in amounts and as a percentage of their total obligations. Leading all BIDs in total dollars expended in support of nutrition research and training were NHLBI, with $60.3 million; NIDDK, with $60.2 million; NCI, with $59.6 million; and NICHD and DRR, with $34.3 million and $22.1 million, respectively. Leading NIH components in terms of percentage of total budget dedicated to support of nutrition research and training were NIDDK, with 11.3 percent; NICHD, with 8.7 percent; DRR, with 6.4 percent; NHLBI, with 6.2 percent; NIEHS with 4.6 percent.

Table 4. Actual Obligations, NIH Biomedical Nutrition Research and Training, as a Percentage of Total BID Obligations, by NIH Component, FY 1988 (in thousands of dollars)

NIH BID	Nutrition Research and Training*	Total BID Obligations**	Nutrition as a Percentage of Total BID Obligations
NCI	$ 59,563	$1,468,435	4.1
NHLBI	60,314	965,283	6.2
NIDR	1,486	126,216	1.2
NIDDK	60,156	534,359	11.3
NINCDS	3,221	534,483	<1.0
NIAID	3,493	638,521	<1.0
NIGMS	2,529	632,624	<1.0
NICHD	34,384	396,584	8.7
NEI	6,879	224,835	3.1
NIEHS	9,914	215,439	4.6
NIA	7,625	194,548	4.0
NIAMS	4,068	147,543	2.8
DRR	22,106	344,150	6.4
FIC	30	15,604	<1.0
NCNR	427	23,361	1.8
Total	**$276,195**	**$6,461,985†**	**4.3**

BID = Bureau/Institute/Division.

*Actual obligations. Source: Human Nutrition Research and Information Management (HNRIM) System data base.

**Obligations. Source: NIH Office of Program Planning and Evaluation.

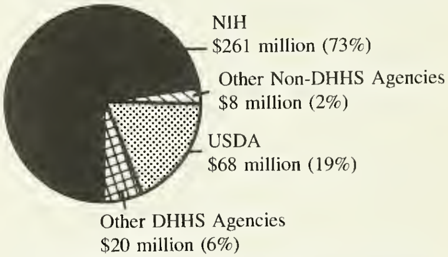
†Total excludes obligations for Office of the Director, National Library of Medicine, and Buildings and Facilities.

Trends in Nutrition Research and Training: 1978-1988

Since 1978, the role of the NIH in federally supported nutrition research and training has grown steadily. In FY 1987, the NIH led all Federal agencies in financial support of nutrition research and training, with a FY 1987 NIH nutrition research and training total of $261 million, as shown in figure 3; this represented 73 percent of all Federal expenditures and 93 percent of all DHHS expenditures in nutrition research and training. NIH nutrition research and training expenditures have consistently represented between 70 and 73 percent of the total Federal expenditure and between 92 and 95 percent of the total DHHS expenditure in nutrition research and training.

NIH nutrition research and training dollars have steadily increased during the past decade, growing from $106 million in FY 1978 to $276

Figure 3. Federal Expenditures in Support of Human Nutrition Research and Training, FY 1987



Source: Human Nutrition Research and Information Management (HNRIM) System data base.

million in FY 1988. Table 5 shows NIH actual obligations for nutrition research and training by BID during the past 10 years; with few exceptions, the trend in dollars has been steadily upward for all institutes, divisions, and centers.

Table 5. Actual Obligations, NIH Biomedical Nutrition Research and Training by BID, FY 1978-1988 (in thousands of dollars)

BID	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988
NCI	$ 18,198	$ 28,303	$ 28,687	$ 30,313	$ 30,553	$ 37,336	$ 50,119	$ 45,199	$ 46,223	$ 52,691	$ 59,563
NHLBI	21,934	28,415	32,184	35,213	35,449	38,350	44,553	45,689	49,265	57,285	60,314
NIDR	2,019	1,663	1,648	1,503	1,529	2,072	1,419	1,795	1,211	1,836	1,486
NIADDK	22,175	25,068	26,457	30,906	26,981	33,332	35,969	45,951	—	—	—
NIDDK	—	—	—	—	—	—	—	—	44,697	54,737	60,156
NINCDS	1,203	2,306	2,837	1,559	2,839	2,547	2,652	2,949	2,158	3,367	3,221
NIAID	765	1,205	1,047	1,562	1,853	1,606	1,646	1,679	1,830	2,652	3,493
NIGMS	2,832	2,971	2,451	2,503	1,841	2,081	2,271	2,307	2,291	2,710	2,529
NICHD	16,292	20,806	20,410	20,108	18,356	20,164	24,152	26,835	27,662	32,932	34,384
NEI	2,664	3,565	4,166	4,265	5,256	5,571	4,611	5,519	5,176	6,545	6,879
NIEHS	3,534	3,540	3,885	2,106	1,582	1,390	1,768	5,366	4,470	12,880	9,914
NIA	1,546	2,628	4,220	4,133	3,261	4,391	4,757	4,608	5,329	6,934	7,625
NIAMS	—	—	—	—	—	—	—	—	2,846	3,424	4,068
DRR	13,136	13,381	11,129	14,330	14,823	15,444	18,874	19,400	19,472	22,089	22,106
FIC	—	—	—	—	—	22	127	19	56	57	30
NCNR	—	—	—	—	—	—	—	—	292	472	427
Total	**$106,298**	**$133,851**	**$139,121**	**$148,501**	**$144,323**	**$164,306**	**$192,918**	**$207,316**	**$212,978**	**$260,611**	**$276,195**

BID = Bureau/Institute/Division.

As seen in table 6, support for nutrition research and training has grown consistently and has comprised 3 to 4 percent of total NIH obligations since FY 1978. Table 6 also shows total NIH biomedical nutrition research and training support in terms of current and constant dollars. For example, nutrition research and training showed a $169 million increase, or 160 percent, in current (unadjusted) dollars between FY 1978 and FY 1988. In constant (adjusted) dollars, however (i.e., in terms of real support), nutrition research and training in FY 1988 represented a 33 percent increase over the FY 1978 level.

Nutrition Research Training

The NIH supports training in biomedical and behavioral nutrition research and training in both the extramural and the intramural programs. Within the extramural program, two basic mechanisms are used for nutrition training support: institutional awards and individual awards. The institutional national research service awards, commonly called "training grants," are designed to enable institutions to make training awards to individuals selected by them for predoctoral and postdoctoral research training. In FY 1988, NIH spent $239 million for persons on training grants. Over $2.6 million (1.1 percent) was expended to train 71 persons in nutrition.

The postdoctoral individual national research service awards, called "fellowships," are awarded to provide postdoctoral research training to individuals to broaden their scientific background and extend their potential for research. In FY 1988, $393,000 was expended for fellowships in nutrition in support of 32 fellows. Within the NIH intramural program, three institutes (the NHLBI, NICHD, and NIDDK) supported training of 15 scientists in nutrition at an expenditure of $190,000 for FY 1988.

NIH EXPENDITURES BY HNRIM CATEGORY AND INTEREST AREA

Table 7 presents the NIH nutrition research support in the 35 HNRIM classification categories and the number of grants or contracts funded in each category. The

Table 6. Actual Obligations, NIH Biomedical Nutrition Research and Training, in Current and Constant Dollars, and as a Percentage of Total NIH Obligations, FY 1978-1988 (in thousands of dollars)

Fiscal Year	Nutrition Research and Training, Current $	Nutrition Research and Training, Constant $*	Total NIH Obligations[†]	Current Nutrition $ as a Percentage of Total NIH Obligations
1978	$106,298	$106,298	$2,828,012	3.8
1979	133,852	123,679	3,184,641	4.2
1980	139,121	117,098	3,428,842	4.1
1981	148,501	113,202	3,572,506	4.2
1982	144,323	101,300	3,643,461	4.0
1983	164,306	108,573	4,013,135	4.1
1984	192,918	120,342	4,493,553	4.3
1985	207,316	122,420	5,121,557	4.0
1986	212,987	120,503	5,296,977	4.0
1987	260,611	140,548	6,175,038	4.2
1988	276,195	140,942	6,610,430	4.2

*Based on biomedical R&D price index, FY 1978 = 100%. Source: *NIH Data Book, 1988,* NIH Publication No. 88, 1261, December 1988.

[†] Source: *NIH Data Book, 1988.* NIH Publication No. 88-1261, December 1988, pp. 8-9.

column labeled "percent of total" represents the funds expended in a given category in relation to total NIH actual obligations for nutrition research and training, which for FY 1988 amounted to $276 million.

A grant or contract may appear in more than one category; if all actual obligations in the 35 categories were summed, the total would be larger than the sum of $276 million. For example, a project on dietary fat may appear under both "Lipids" and "Cardiovascular Disease and Nutrition."

While NIH nutrition research encompasses all 35 classification categories, the largest component of NIH nutrition research is concentrated in area I, Research in the Biomedical and Behavioral Sciences (codes 1 through 25 and code 35).

NUTRITION RESEARCH AND TRAINING SUPPORT MECHANISMS

Nutrition research at the NIH includes studies in biochemistry, physiology, cell biology, and epidemiology; intervention and demonstration projects; clinical trials; and others that attempt to better elucidate the fundamental mechanisms of action of nutrients during normal growth and development as well as in patients suffering from specific diseases. These results are then synthesized into practical nutrition information necessary to educate the individual and help him or her live a long and healthy life. New and better methods of transmitting the latest scientific knowledge concerning nutrition are continually being sought. Initiatives in this area include the National Cholesterol Education Program and National High Blood Pressure Education Program (NHLBI) and the Cancer Awareness Program (NCI).

Like the rest of the NIH budget, NIH nutrition research and training expenditures support two broad categories of research: extramural and intramural. The extramural programs are responsible for roughly 80 percent of NIH resources in the form of research grants or contracts. Through these programs, NIH makes approximately 26,000 awards of various kinds to institutions throughout the U.S. and the world. Extramural awards are based on a two-tiered peer review assessment--one for scientific merit and one for program relevance.

Within the NIH itself, and accounting for approximately 13 percent of its budget, is the intramural research program. All of the NIH institutes except NIGMS have an intramural component of laboratory and clinical research programs. Over 2,500 research projects are in progress at all times, making the NIH the largest center for biomedical and behavioral research in the world. Boards of scientific

Table 7. Actual Obligations, NIH Biomedical Nutrition Research and Training, by HNRIM Classification Category, FY 1988

Nutrition Research Classification		Number of Grants and Contracts	Actual Obligations* (in thousands of dollars)	Percent of Total**
Code	Area			
1	Maternal Nutrition	154	$18,573	7
2	Infant and Child Nutrition	280	38,256	14
3	Adolescent Nutrition	57	9,166	3
4	Adult Nutrition	55	7,053	3
5	Nutrition of the Elderly	90	10,324	4
6	Cardiovascular Disease and Nutrition	431	71,657	26
7	Cancer and Nutrition	487	62,484	23
8	Other Diseases and Nutrition	505	56,139	20
9	Trauma (Burns) and Nutrition	25	3,174	1
10	Infection, Immunology, and Nutrition	122	16,418	6
11	Obesity, Anorexia, and Appetite Control	287	35,527	13
12	Genetics and Nutrition	188	28,747	10
13	Nutrition and Function	178	25,074	9
14	Nutrient-Nutrient/Drug/Toxicant Interactions	309	35,329	13
15	Other Conditions and Nutrition	589	55,485	20
16	Research on Nutritional Status	177	28,493	10
17	Carbohydrates	146	18,491	7
18	Lipids (Fats and Oils)	408	72,453	26
19	Alcohols	39	3,177	1
20	Proteins and Amino Acids	290	37,792	14
21	Vitamins	425	57,814	21
22	Minerals and Trace Elements	339	45,008	16
23	Water and Electrolytes	118	19,193	7
24	Fiber	26	5,608	2
25	Other Nutritents in Food	61	5,760	2
26	Food Consumption	42	8,264	3
27	Bioavability	35	6,299	2
28	Effects of Technology on Food/Diets	38	4,388	2
29	Other Research in Food Science	27	1,989	1
30	Food Consumption Surveys, R&D	21	5,956	2
31	Research on Dietary Practices, Food Consumption, etc.	183	29,982	11
32	Methods for Educating and Informing the Public	37	10,287	4
33	Other Research in Nutrition Education	10	573	<1
34	Effects of Government Policy and Socioeconomic Factors	4	28	<1
35	Parenteral, Enteral, and Elemental Nutrition	84	15,202	6
51	Prevention of Disease	631	66,372	24
52	International Research	29	4,537	2
53	Epidemiological Research	66	10,083	4
54	Education for Professionals	29	2,536	1
55	Education for the Public	5	1,190	<1
56	Clinical Trials	124	17,836	6

*A grant or contract may be assigned to more than one of these areas.

**The total expenditure of the NIH nutrition program in FY 1988 was $276,195,000.

counselors are responsible for assessing the quality and direction of the intramural program, and the Office of the Director provides scientific and policy oversight.

The NIH relies on three major funding mechanisms as the administrative instruments for accomplishing its program goals through the efforts of scientists outside the NIH (i.e., extramurally): grants and cooperative agreements (financial assistance awards) and contracts (acquisition awards). Appendix C gives details on NIH award mechanisms. Financial support of extramural nutrition research and training at the NIH is provided through all three of these major funding mechanisms. Support of extramural nutrition research utilizes research project grants, program project grants, center grants, contracts, and cooperative agreements, all of which may include clinical trials; research resources support; reimbursement agreements; research career development awards (RCDA's); and new, academic, and teacher investigator awards. Extramural training in biomedical and behavioral nutrition research is supported through national research service awards, with training grants awarded to institutions and fellowships awarded to individuals. The intramural nutrition program consists of research projects and training.

Table 8 presents NIH FY 1988 actual obligations in biomedical nutrition research and training by category of support. Of the $276 million expended by the NIH in FY 1988 in support of nutrition research and training, 95 percent supported extramural projects. Research grants comprised the largest category, with 1,586 projects supported at an expenditure of $167 million; of these, 100 projects, with an expenditure of $12 million, were clinical trials. Program projects formed the next largest category, with 79 projects (7 clinical trials) at a cost of $30 million ($2.5 million for clinical trials). Research resources support was the third largest category, at 306 projects and $22 million.

CLINICAL NUTRITION RESEARCH UNITS

Advances in the knowledge of human biochemistry and physiology have placed clinical nutrition on a sound scientific base. Many nutritional deficiency states, consequences of inborn errors of metabolism, and food-related diseases are now understood, and may be treated or prevented. However, there remain many unanswered questions on the relationship of diet to health, to acute diseases, to chronic diseases, to development and to aging.

Advances in research to help answer questions about nutrition and disease are derived from many disciplines (such as biochemistry, molecular biology, genetics, and physiology) and medical specialties (such as internal medicine, pediatrics, and surgery). Nutritional sciences are interdisciplinary and are dependent on close interactions among research investigators, health service providers, and educators.

As a means of encouraging a multidisciplinary approach to clinical nutrition research, the NIH has sought to foster the development and operation of clinical nutrition research units (CNRUs) through the establishment of a CNRU program in 1979. Two NIH institutes, the NCI and NIDDK, are supporting these units. Specific objectives of a CNRU are:

- To create or strengthen a focus in a biomedical research institution for multidisciplinary research in clinical nutrition, in order to develop new knowledge about specific nutrients in health throughout the human life cycle, and in the prevention and treatment of disease.
- To strengthen training environments in order to improve the education of medical students, house staff, practicing physicians, and allied health personnel in clinical nutrition.
- To enhance patient care and promote good health by focusing attention on clinical nutrition and generating nutritional information for the public.

The essential components of a CNRU are:

- Research with human subjects and populations;
- Laboratory investigations;
- Research training (funds derived from other sources);
- Shared facilities and research resources;
- Education programs for medical students, house staff, practicing physicians, and allied health personnel (funds derived from other sources);
- Research components of nutritional support services; and
- Public information activities (funds derived from other sources).

To qualify for the award of a CNRU grant, the potential applicant institution must already have a substantial base of ongoing, independently supported peer-reviewed research in the nutritional sciences. This initial required research base is formed from a group of investigators with individually funded research projects who can benefit from shared resources. Thus, the CNRU grant is intended to provide an added dimension that includes the capability and the potential for accomplishments greater than that possible by the support of individual projects alone.

Table 8. Actual Obligations, NIH Biomedical Nutrition Research and Training, by Category of Support, FY 1988 (in thousands of dollars)

Funding Mechanism	Item	Breakdown		Total	
		Number	Cost	Number	Cost
Extramural					
Research Grants	Regular	1,486	$154,698		
	Clinical Trials	100	12,078		
	Total			1,586	$166,776
Program Projects	Regular	79	27,658		
	Clinical Trials	7	2,500		
	Total			86	30,158
Contracts	Regular	120	18,313		
	Clinical Trials	9	1,788		
	Total			129	20,101
Centers	Regular	40	13,214		
	Clinical Trials	1	174		
	Total			41	13,388
Research Resources Support				306	22,118
Reimbursement Agreements				22	3,844
Career Development Awards				74*	2,677
New Investigator Research Awards				25*	601
Training	Training Grants	39*	2,235		
	Fellowships	32*	393		
	Total			71*	2,628
Subtotal, Extramural					262,291
Intramural					
Projects				98	13,714
Training				15*	190
Subtotal, Intramural					13,904
Total NIH Biomedical Nutrition Research and Training					$276,195

*Number of training grants

The major source for support of biomedical research projects associated with the CNRU is derived from the separately funded projects of the participating investigators. Similarly, stipends for professional trainees in research are not available through CNRU funding; rather, such funding must be sought through other funding mechanisms.

As indicated above, any institution or consortium wishing to qualify for the CNRU grant award must have an active program of excellence in basic and clinical biomedical research in nutrition and/or nutritional sciences at the time of submission of an initial application. The biomedical research base is the prerequisite for the establishment of a

Table 9. Clinical Nutrition Research Units – Scientific Core Facilities

University of California, Davis
Vitamin and Mineral (analysis) Core
Metabolism Core
Cell Biology Core
Food Biology Core
Clinical Support Core

University of Alabama in Birmingham
Vitamin (analysis) Core
Nutrient Metabolism Core
Cell Biology Core
Clinical Support Core
Nutrition Education Core

Memorial Sloan-Kettering Cancer Center
Biophysics Core
Immunology Core
Metabolism and Metals Core
Lipids Core
Metabolic Bone Disease Core

University of Washington
Clinical Assays Core
Nutrition Laboratory Core
Clinical Nutrition Research Core
Administrative Core

University of Wisconsin
Analytical Core
Clinical Core
Clinical Nutrition Laboratory Core
Administrative Core

Harbor-UCLA Medical Center
Lipid and Hormone Core
Stable Isotope Core
Vitamin and Trace Element Core
Mutagenesis Core

University of Chicago
Vitamin Assay Core
Nutritional Assessment Core
Mineral/Trace Element Core
Lipid/Lipoprotein Core
Radioimmunoassay Core
Study Design and Data Management

Vanderbilt University
Mass Spectrometry Core
Laboratory Core
Nutrition Support
Intestinal Transport Core
Nutrient Transport Core
Energy Balance Core

CNRU and when established is the most important component. The research base will be given primary consideration in the peer review process. Focus, relevance, interrelationships, and productivity are all considerations in judging the adequacy of the research base.

Eligibility for an award is limited to domestic institutions.

CNRU Research Core Facilities

Core facilities of CNRUs are developed to support research in the broad areas of fundamental and clinical nutrition.

Application of state-of-the-art techniques in the areas of cell biology, molecular biology, immunology, and integrative physiology is encouraged to increase knowledge concerning the function and requirements of nutrients, the relationship of diet (and nutrients) to health and disease, and the prevention and treatment of disease as an outgrowth of nutrition research.

The fundamental research supported by the NIDDK and NCI has generally been nutrient-centered rather than focused on a particular disease, organ, or life cycle. In contrast, the clinical investigations usually concern problems interrelating nutritional status with the biochemical and physiological function of a cell population, organs, or the whole individual. A list of CNRU facilities is given in table 9.

A CNRU must be an identifiable organizational unit within a single university medical center or a consortium of cooperating institutions. The overall goal of the CNRU is to bring together, on a cooperative basis, basic science and clinical investigators in a manner that will enrich the effectiveness of research in nutritional sciences. A program of excellence in biomedical research in this area must be in existence at the time of submission of a CNRU application. Close cooperation, communication, and collaboration among all center personnel of many professional disciplines are characteristics of a successful CNRU. A successful CNRU will also attract into the CNRU talented scientists from disciplines other than nutrition.

Core facilities in a CNRU are shared resources that enhance productivity or in other ways benefit a group of investigators working to accomplish the stated goals of the CNRU. Two other types of activities may also be supported with CNRU funding--a pilot and feasibility program and an enrichment program. The pilot and feasibility program provides modest support for new initiatives or feasibility studies for new investigators or for established investigators who are in research areas of direct interest to the CNRU. These areas may include biomedical, epidemiologic, or behavioral research as they pertain to the CNRU goals. The enrichment program provides limited funds to sponsor seminars, visiting scientists, workshops, etc.

NATIONAL NUTRITION MONITORING RESEARCH

To assess the nutritional status of Americans, particularly as related to health and mortality outcomes, a series of National Health and Nutrition Examination Surveys (NHANES) was begun in 1971. Conducted during 1971 to 1974 and 1976 to 1980, respectively, NHANES I and II constituted the largest in-depth national survey, until now, of health and nutrition ever made on a representative sample of the U.S. population. NHANES III, scheduled for 1988 to 1994, will provide a much-needed updating of this critical information.

National Health and Nutrition Examination Surveys

Conducted by the National Center for Health Statistics (NCHS), each NHANES consists of a series of surveys of probability samples of the population, each comprising over 20,000 U.S. residents. The surveys include physical examination, anthropometry, blood cell assessments, biochemical analyses of blood and urine, x-rays, functional assessment, health histories, and dietary intake interviews. As in all long-term, longitudinal studies, respondents are traced and reexamined; information is obtained from hospital records, the National Death Index, and death certificates. The resulting data provide national estimates of diseases and of health, and nutritional characteristics of the U.S. population and selected subgroups.

NHANES III is also planned as a longitudinal study with morbidity and mortality endpoints. The survey will "oversample" older persons. That is, approximately 7,000 persons age 60 and older will be included; of this group, about 1,000 will be age 80 and older. Blacks, Mexican-Americans, and Puerto Ricans will be heavily represented in the general survey.

The NIH supports NHANES in several ways. NIH-supported scientists participate in the planning of each NHANES survey. The NIH devotes research funds to improving methods and techniques of measuring dietary intake, to fine-tuning biochemical and clinical indices of nutritional status, and to perfecting other assessment and monitoring parameters. Each year NIH institutes fully or partially support NHANES followup surveys. During years of the survey itself, NIH institutes fund both the survey and followup activity. For example, in FY 1988 the NIH provided $2.4 million to NCHS for NHANES.

The NIA is collaborating with the NCHS to fund acquisition of additional dietary intake information from older participants. The NHLBI will continue funding lipoprotein analysis and survey measurements that assess cardiovascular risk factors. The NICHD plans to support methodology to investigate growth relationships and dietary intake. The NIAMS plans to support the development of methodology to investigate osteoporosis risk factors. The NIDDK plans to fund measurements related to gallstones, kidney disease, and diabetes. The NIDR will continue to fund the oral health examination and questionnaire component. Eight NIH institutes (the NCI, NHLBI, NIDR, NIDDK, NIAID, NICHD, NIA, and NIAMS) contribute to NHANES regularly.

The NIA in conjunction with the NCHS is conducting a follow-back study of the NHANES III to collect additional nutrition data from the survey's respondents over 60 years of age. This supplement will collect ancillary nutrition data beyond that included in the main body of the NIA-NCHS intra-agency agreement for the NHANES III.

The NHANES series is the only source of nutrition, health, and aging data on a representative sample of the U.S. The third (NHANES III) will collect health and dietary information on the very old (above age 75 years) for the first time, yielding a comprehensive resource for aging research. The dietary intake instruments (a 24-hour recall, a non-quantitative food frequency, a dietary supplement questionnaire, and an eating habit questionnaire) are being augmented with two additional 24-hour recalls, patterned to account for daily and seasonal variation. These data will make the survey appropriate for the estimation of relationships between diet and health and make NHANES III a primary research tool for studying common diet related diseases and conditions of old age.

The two additional recalls will be administered by telephone, using the same computerized recall questionnaire and interviewing techniques used for the in-person 24-hour recall obtained in the examination trailers. In addition to obtaining intake data on diet for the previous day, the in-trainer interview will also be used as a training session for the subsequent telephone interviews. The three recalls for each respondent will be averaged to give an estimated daily mean for food and nutrient intake.

The NIH derives significant research advantage from NHANES data. Various institutes perform followup studies using NHANES data to test hypotheses about the relationship of dietary practices to the incidence of cancer, heart disease, obesity, osteoporosis, and kidney disease, as well as to study the effect of diet on overall health and longevity.

Examples of NIH-supported NHANES followup studies include:

- An NCI biometric study is analyzing raw data files of NHANES II to discern a profile of the impact of the major cancer risk factors, i.e., smoking, diet, and occupation. In addition to utilizing the NHANES multiple risk factor analysis, NCI-supported investigators are examining the major risk factors separately, as appropriate, as well as looking at particular pairs of risk factors, to create a database of potential use to other disease-oriented investigators, especially those studying heart disease.
- During 1982 through 1984, an initial followup was conducted of the 14,000 persons 25 through 74 years old at the time of the original NHANES I. This NHANES I followup began as a joint project of NIA and the NCHS, but has since received input and financial support from several other NIH institutes. The NCI is supporting research to examine the relation of dietary iron and certain biochemical markers of iron stores with the subsequent long-term risk of cancer. In addition, the study is measuring the interaction of the "oxidant" iron with antioxidants, such as vitamins C and E. Another study is looking at selected cohorts from surveys such as NHANES I and is following these individuals for cancer morbidity and mortality. Laboratory measures of nutritional status are being incorporated into selected case control studies. The NHLBI supports studies of secular trends in cardiovascular risk factors using representative samples of individuals from NHANES I and II and the Hispanic NHANES. Trends will be determined over time in the conventional risk factors, serum cholesterol, blood pressure, cigarette smoking, and obesity. In addition, data from contemporaneous surveys of special segments of the populations with different life styles (Hispanic Americans and USAF personnel) will be compared to data from NHANES II. The NICHD is supporting studies to develop statistical multiple linear regression models that can be applied to NHANES I and II data sets in order to analyze relationships between nutrition variables, body measurements, and blood chemistries. For the first time an evaluation of diet intake of Americans over 75 is under way. The NIA, in conjunction with the NCHS, will conduct a follow-back study of the NHANES III to collect additional nutrition data from the survey's respondents over 60 years of age. Plans are in progress to test the computerized 24-hour recall system and the telephone followup using BLSA participants.

Other examples of NIH nutrition research related to the NHANES surveys are as follows:

- Testing of various hypotheses on the relationship of diet to the incidence of disease(s).
- Regression analyses to determine standardized stratum-specific patterns of fat consumption by age, race, sex, and so forth, as well as descriptive data on national cooking practices, numbers of meals eaten per day, and other factors.
- Studies of various relationships of diet (vitamins A and C, carotene, and fiber) and incidence and mortality from various types of cancer (colon, rectal, lung, prostate, and breast).
- Assessment of dietary and anthropometric data as predictors of age at menarche and in relation to the development of breast cancer.
- Exploring relationships of ingesting artificial sweeteners, saccharin, and cyclamates and incidence and mortality from kidney and bladder cancer.
- Correlations of obesity and nutrition (ponderal index), dietary fat, cholesterol, fiber, and so forth, and the incidence of gallstones and gallbladder cancer.
- Evaluations of the role of diet in benign breast disease.
- Studies of caffeine ingestion and cancers of the bladder and pancreas.

- Elucidation of trends in vitamin usage across the country by age, sex, exercise, Quetelet's index, etc.
- Studies of the relationship between infants' milk intake and their serum cholesterol.
- Investigations of factors in the diet (cholesterol, fat, sodium, calcium, magnesium, and potassium) as they affect cerebrovascular disease, coronary heart disease, and hypertension.
- Assessment of dietary patterns of older persons as related to morbidity, disability, and mortality.
- Evaluation of diet and nutritional factors on the mental health status of older persons.

Other NIH-Supported Nutrition Surveys

In addition to the NHANES series, the NIH supports or undertakes other valuable nutritional surveillance efforts. The following are a few examples:

- Cholesterol Awareness Survey (NHLBI and FDA), conducted among physicians and other U.S. adults, 1983 and 1986.
- Nursing and Dietitian Surveys (NHLBI), to be conducted among U.S. nurses and dietitians.
- Vitamin/Mineral Supplements in Cancer Control (NCHS and NCI), 1988.
- Physician Knowledge Survey on Hypertension (NHLBI), 1978-1988.
- Cancer Prevention Awareness Program (NCI), conducted among U.S. adults started in 1984 and is ongoing.

Food Composition Methodology

In order to fill potential gaps in the information provided by other agencies, several NIH institutes undertake studies which include analysis of the nutritional content of food. A few such examples follow:

- Dietary fiber and fiber components, carotenoids, vitamin A, and selenium analysis (NCI).
- Taurine, pyridoxine beta glucoside, molybdenum, and biotin analysis (NIDDK).
- Development of methods for determining nutrients in human colostrum and milk (NICHD).
- Mutagens from the cooking of foods (NIEHS).
- Food fatty acid analysis and evaluation (NHLBI).
- USDA Services for Nutrient Composition Laboratory (NHLBI). This interagency agreement supports the development of new or improved techniques for analysis of nutrients.

Computerized Nutrient Data Sources

Examples of NIH-supported nutrient data bases include the following:

- *Food Component Research Database.* The NCI in collaboration with the Food and Drug Administration, as well as several European countries are adapting and extending the factored Food Vocabulary (FFV), into a standardized description of food items in the world food supply. A prototype food component research database, indexed by the FFV, and containing numeric and bibliographic data on the content of nutrients, additives, contaminants and naturally occurring substances in foods, is being developed in consultation with a number of international experts. This comprehensive data system will provide a valuable research tool for investigators conducting dietary interventions, clinical trials, and epidemiological studies on the relationship between dietary components and cancer risk and will serve as a resource of information essential for the formation of public policy on diet-related public health issues.
- *Nutrition Coordinating Center.* The NHLBI supports a standardized system for collecting, coding, processing, and analyzing dietary information. The information in the interactive, computer database is from the USDA, other standard references, and food manufacturers. The coding manual and nutrient database are continually updated by a staff of nutritionists and data specialists to reflect changes in the marketplace. This system has been extensively field-tested in studies across North America since 1974.
- *USDA Nutrient Data Bank.* The NHLBI supports the continued development of the USDA Nutrient Data Bank and the USDA revision of Agriculture Handbook No. 8, Composition of Foods. Raw, Processed, Prepared. This funding is specifically directed to the compilation of accurate food composition data for nutrients associated with heart, lung, and blood diseases (lipids, carbohydrate fractions, trace elements, and amino acids).

INTERNATIONAL PROGRAMS IN NUTRITION RESEARCH

NIH's international nutrition research programs are organized at two levels. The first level involves country-to-country agreements on science or health, usually bilateral or multilateral formal intergovernmental agreements. The second level is based on less formal, technical-level agreements between the NIH or specific institutes at the NIH and counterpart foreign institutions; these agreements are usually confined to discrete research subjects.

The Fogarty International Center (FIC) represents the NIH in contacts with multilateral bodies such as the World Health Organization (WHO), Pan American Health Organization (PAHO), European Science Foundation (ESF), Organization for Economic Cooperation and Development (OECD), and Commission of the European Communities.

On matters of worldwide concern, the Director of the NIH participates in international conferences and in meetings with officials of foreign governments. Such meetings establish initial contacts that often evolve into long-term relationships with scientists and organizations in other countries.

International agreements on nutrition research by institutes and divisions of the NIH provide research information of significance in the effort to prevent or control disease problems here and abroad. Among the NIH units participating in this important effort are the following:

- The NCI participates with the government of Finland in a three-pronged cooperative project to determine if either beta-carotene or alpha-tocopherol supplementation individually or in combination is effective in preventing lung cancer in smokers; to assess the role of fats, selenium, and vitamins A, E, and C on breast cancer development; and to evaluate the relationship of intake of various nutrients to subsequent cancer development.
- The epidemiology and prevention of cardiovascular and cardiopulmonary diseases is under study in a U.S.-China program begun in 1981 and supported by the NHLBI. The study population of more than 11,000 Chinese steel workers, farmers, and shipyard workers is targeted for interventions directed at smoking behavior, intake of fats and salt, and other factors. To date, the study shows the blood cholesterol levels of all Chinese population groups to be significantly lower than those found in the U.S.
- A cooperative effort in the Federal Republic of Germany to reduce cardiovascular mortality is based on the methods used in the U.S. National High Blood Pressure and/or National Cholesterol Education Program. Extensive campaigns were carried out through print and electronic media to increase public awareness; free blood pressure screenings were made available. Low-salt, fat modified foods were also made available in cafeterias, restaurants, and bakeries.
- Japan and the U.S. share a high prevalence of hypertension, but in Japan, stroke is more common than heart attack. Under a cooperative agreement with Japan, an inbred spontaneously hypertensive rat developed for U.S. research is now used in Japanese studies of the protective potential of a low-salt, high-protein diet.
- U.S.-U.S.S.R. collaborations in nutrition research are centered on cardiovascular health and disease. The pathogenesis of arteriosclerosis is studied in basic and clinical research investigating lipoprotein/atherosclerosis interactions. Epidemiologic studies, including the U.S.-U.S.S.R. joint Lipid Research Clinics studies, are now conducted within the U.S.-U.S.S.R. program area of Cardiovascular Epidemiology and Prevention.
- The NEI collaborates with the National Institute of Nutrition in Hyderabad, India, in an applied clinical research program to identify children who are at risk of becoming blind from hypovitaminosis A and other factors, and to determine practical ways to provide vitamin A prophylaxis.
- Other NEI studies of vitamin A deficiency (xerophthalmia) in India included evaluation of the risk of respiratory and diarrheal disease among children living in areas highly endemic for vitamin A depletion and night blindness.
- The NEI has collaborated with the Indian Council of Medical Research and the Rajendra Prasad Ophthalmic Center in New Delhi to study dietary and other risk factors in the development of age-related cataract. The results of this case control study are being compared with similar

studies ongoing in Parma, Italy and in Boston.

- In May 1988, the World Health Assembly called for the establishment of an international research program on aging as an integral part of the WHO Global Program on Health of the Elderly. The Special Program for Research on Aging (SPRA) is based at the WHO Collaborating Center for Research on Aging, located at the NIA on the Bethesda campus. The program is being organized in two areas: research and development; and strengthening of national research. Initially the research focus is on four scientific priorities: determinants of healthy aging; age-associated dementias; age-related changes in immune function; and nutritional changes associated with aging. The first nutrition-related area selected for worldwide emphasis is osteoporosis. This international initiative will include four studies. The first will be an assessment of the world wide prevalence of osteoporosis as measured by the rate of osteoporotic fractures in selected countries. Using a sample drawn from the first study, data will be collected on the characteristics of bone density and bone turnover. The third study will be an epidemiologic investigation to determine primary and/or universal risk factors (hormonal, nutritional, and environmental) associated with osteoporotic fractures. The final and perhaps the most important study will be the implementation of interventions to retard or prevent osteoporotic fractures which have been derived from data collected in the first three studies.
- The NIAID is collaborating with investigators in many countries on studies of rotaviruses, the single most important group of etiologic agents that produce severe diarrhea in infants and young children in the U.S. and abroad, in both industrialized and developing countries. Field trials of a preventive vaccine developed by NIAID-supported investigators have been conducted in the United States and are under way or planned in Chile, Finland, India, Pakistan, Sweden, and Venezuela. To date, the most promising results are from Venezuela, where vaccine efficacy was 93 percent in 1- to 5-month-old infants, and 100 percent for severe rotavirus diarrhea in all age groups.
- NIAID-supported scientists, collaborating with investigators at the Kenya Medical Research Institute, studied urinary schistosomiasis infections and growth patterns among children. The investigators found that treatment with metrifonate appears to lessen anemia and to improve child growth rates, despite the prevalence of protein-energy malnutrition.
- The NIDDK is presently the lead institute for the U.S.-Japan Malnutrition Panel of the U.S.-Japan Cooperative Medical Science Program. It supports research on the nutritional significance of varying polyunsaturated fatty acids in the diet, nutritional aspects of bone disease, endogenous mediators of nutritional metabolism, and improved methods of nutritional assessment. With the westernization of dietary patterns, Japan has experienced a change in nutritional status and an increase in nutrition-related diseases. The impact of the change in dietary patterns and development of disease is being investigated.
- A NIDDK study being undertaken with India concerns the formulation of upper and lower urinary tract stones. Dietary factors are among those being studied. They will include assessment of fluid intake and water content of food, and dietary amounts of calcium, phosphorus, magnesium, and sodium.
- DRS's laboratory animal nutrition program, operating in conjunction with the PAHO, assists in developing diets for nonhuman primates maintained in conservation and breeding programs in several South American countries. This activity includes the formulation of nonhuman primate diets that use ingredients readily available in areas where captive primate colonies have been established. The vitamin and mineral premixes for these diets are manufactured in the United States.
- The NIDR participates in the WHO in the International Collaborative Study of Oral Health Outcomes, designed to provide critical information on comparing the effectiveness and efficacy of various national strategies for enhancing oral health.

- The NIDR-supported dental investigators at the University of Alabama and scientists at the Universidad Peruana Cayetano Heredia have shown that chronic malnutrition (stunting) occurring in Peruvian children, as opposed to acute malnutrition (wasting), has been specifically associated with delayed tooth eruption and exfoliation, which appear to render the deciduous teeth more susceptible to dental caries.

Appendices

APPENDIX A

LEGISLATIVE BASE FOR NUTRITION AT THE NIH

On November 20, 1985 the Health Research Extension Act of 1985 became Public Law 99-158. This act amended the Public Health Service Act "...to revise and extend the authorities under that Act relating to the National Institutes of Health and for other purposes."

Four institutes--the National Cancer Institute (NCI); National Heart, Lung, and Blood Institute (NHLBI); National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); and National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)--have specific mandates to conduct nutrition research at the NIH. These mandates are as follows:

NCI. Section 413(a)--"establish an information and education center to collect, identify, analyze, and disseminate on a timely basis, through publications and other appropriate means, to cancer patients and their families, physicians and other health professionals, and the general public, information on cancer research, diagnosis, prevention, and treatment (including information respecting nutrition programs for cancer patients and the relationship between nutrition and cancer)...."

NHLBI. Section 420--"(1)...dissemination of information regarding diet and nutrition, environmental pollutants, exercise, stress, hypertension, cigarette smoking, weight control, and other factors affecting the prevention of arteriosclerosis and other cardiovascular diseases and of pulmonary and blood diseases; and (2) the dissemination of information designed to encourage children to adopt healthful habits respecting the risk factors related to the prevention of such diseases...."

Section 421(a)(1)(A)--"investigation into the epidemiology, etiology, and prevention of all forms and aspects of heart, blood vessel, lung, and blood diseases, including investigations into the social, environmental, behavioral, nutritional, biological, and genetic determinants and influences involved in the epidemiology, etiology, and prevention of such diseases...."

NIDDK. Section 426--"conduct and support of research, training, health information dissemination, and other programs with respect to diabetes mellitus and endocrine and metabolic diseases, digestive diseases and nutritional disorders, and kidney, urologic, and hematologic diseases...."

Section 428--"(a)(1) In the Institute there shall be a Division Director for Diabetes, Endocrinology, and Metabolic Diseases, a Division Director for Digestive Diseases and Nutrition...responsible for--(A) developing a coordinated plan (including recommendations for expenditures) for each of the national research institutes within the National Institutes of Health with respect to research and training concerning diabetes, endocrine and metabolic diseases, digestive diseases and nutrition, and kidney, urologic, and hematologic diseases; (B) assessing the adequacy of management approaches for the activities within such institutes concerning such diseases and nutrition and developing improved approaches if needed; (C) monitoring and reviewing expenditures by such institutes concerning such diseases and nutrition; and (D) identifying research opportunities concerning such diseases and nutrition and recommending ways to utilize such opportunities...(b)(1) carry out programs of support for research and training (other than training for which National Research Service Awards may be made under section 487) in the diagnosis, prevention, and treatment of diabetes mellitus and endocrine and metabolic diseases, digestive diseases and nutritional disorders, and...(2) establish programs of evaluation, planning, and dissemination of knowledge related to such research and training."

Section 432--"There are established within the advisory council for the Institute appointed under section 406 a subcommittee on diabetes and endocrine and metabolic diseases, a subcommittee on kidney, urologic, and hematologic diseases....The subcommittees are authorized to review applications made to the Director of the Institute for grants for research and training projects relating to the diagnosis, prevention, and treatment of the diseases for which the subcommittees are established and shall recommend to the advisory council those applications and contracts that the subcommittees determine will best carry out the purposes of the Institute. The subcommittees shall also review and evaluate the diabetes and endocrine and metabolic diseases, digestive diseases and nutrition, and kidney, urologic, and hematologic diseases programs of the Institute and recommend to the advisory council such changes in the administration of such programs as the subcommittees determine are necessary."

NIAMS. Section 440(6)--"...projects for investigation into the epidemiology of all forms and aspects of arthritis and musculoskeletal diseases, including investigations into the social, environmental, behavioral, nutritional, and genetic determinants and influences involved in the epidemiology of arthritis and musculoskeletal diseases...."

Other institutes that conduct and support nutrition research do so under much broader authority. Each conducts research programs in the "diagnosis, prevention, and treatment" of specific diseases and life processes within their areas of responsibility. These authorities are as follows:

- National Institute of Dental Research (NIDR): Section 453
- National Institute of Neurological and Communicative Disorders and Stroke (NINCDS): Section 457
- National Institute of General Medical Sciences (NIGMS): Section 461
- National Institute of Child Health and Human Development (NICHD): Section 448
- National Eye Institute (NEI): Section 455
- National Institute of Environmental Health Sciences (NIEHS): Section 463
- National Institute on Aging (NIA): Section 444
- Division of Research Resources (DRR): Section 480 (supporting research resources)
- International Cooperation Authority: Section 482
- Training Authority: Section 487

NIDDK (Section 427) has established two clearinghouses, the National Digestive Diseases and Nutrition Clearinghouse and the National Kidney and Urologic Diseases Information Clearinghouse, and NIAMS (Section 438 (b)) has established the National Arthritis and Musculoskeletal and Skin Diseases Clearinghouse to facilitate and enhance the distribution of information regarding these specific disease areas to health professionals, patients, and the public. Nutrition information is often included.

In order to place more emphasis on research on health maintenance and disease prevention, the Health Research Extension Act of 1985 established the appointment of an Associate Director for Disease Prevention within the NIH Office of the Director, NCI, and NICHD. A similar position exists at NHLBI by current law. The associate directors are to "assure that each Institute's research plans include sections dealing with such prevention-related research as investigations into the epidemiology of disease; studies of the etiology of diseases (including the effect of diet and other personal habits on the development of disease, and the effect of environmental factors, including air, water, radiation, and toxic substances, on the development of disease); research into immunizations against disease; studies of the means to preclude the development of disease through changes in personal habits and environmental factors; and studies of methods for, and the cost-effectiveness of, population screening programs." The Associate Director for Disease Prevention within the Office of the Director, NIH, is responsible for promoting and coordinating the research programs of all institutes regarding the prevention of disease. In 1986, NIH established the Office of Disease Prevention (ODP) within the Office of the Director, under the purview of the NIH Associate Director for Disease Prevention.

APPENDIX B

NCC-SPONSORED SCIENTIFIC SEMINARS, FY 1988

FY 1988

USDA Nutrient Data Bases
Betty Perloff, Nutritionist, Human Nutrition Information Service, USDA

Dietary Energy Expenditure and Obesity in Man
Clifton Bogardus, III, M.D., Chief, Clinical Diabetes and Nutrition Section, Phoenix Epidemiology and Clinical Research Branch, Division of Intramural Research, NIDDK

Exercise and Nutrition: Effects on Protein Metabolism and Requirements
William J. Evans, M.D., Chief, Human Physiology Laboratory, USDA Human Nutrition Research Center on Aging, Tufts University, Boston, Massachusetts

Nutritional Consequences of AIDS
Donald Kotler, M.D., Associate Professor of Clinical Medicine, St. Luke's Roosevelt Medical Center, New York

Integration of Information Systems via an Interactive Thesaurus
Bradley Rosenthal, Associate Director for Management, and George Brindza, Computer Systems Branch, Center for Food Safety and Applied Nutrition, FDA

Update on Plans for NHANES III
Catherine Woteki, Ph.D., National Center for Health Statistics/CDC

The Role of Vitamin A and Low-Birth-Weight Infants
Mildred Stahlman, M.D., Vanderbilt University School of Medicine, Nashville, Tennessee

APPENDIX C

NEW PROGRAM ANNOUNCEMENTS, REQUESTS FOR APPLICATIONS AND REQUESTS FOR PROPOSALS IN NUTRITION AND NIH GRANT MECHANISMS, FY 1988

Program Announcements, Requests for Applications, and Requests for Proposals

A major responsibility of the DNRC and its NCC is to identify areas for further research and bring them to the attention of the institutes for the developments and publications of program announcements (PAs), requests for applications (RFAs), and requests for proposals (RFPs). When areas of nutrition research are of interest to more than one institute, including those of Alcohol, Drug Abuse, and Mental Health Administration, joint PAs are often developed under the auspices of the NCC.

- A PA is a formal statement of an NIH extramural research activity or of the initiation of a new or modified mechanism of support. It may describe new or modified program interests, or simply be a reminder of continuing interest.

- An RFA is a formal statement that invites grant applications in a well-defined scientific area to accomplish specific program purposes, generally identifies only one application receipt date, and indicates whether or not funds have been set aside for the competition and, if so, the amount of funds and/or the expected number of awards to be made. An RFA may be reissued as necessary.

- An RFP is the government's invitation to propective offerors to submit a contract proposal based on the terms and conditions set forth in the RFP by the statement of work that describes the nature of intended procurement. The number of contracts awarded as a result of an RFP is smaller than the number of application funded as a result of PAs and RFAs. PAs, RFAs, and RFPs in Nutrition Research and Training published in the *Guide for Grants and Contracts* in FY 1988 follow in chronological order.

FY88 RFAs, RFPs, and PAs:

Issued By	Date	Type	Title
NCI	10/87	RFA	Cooperative Agreements for Prevention Clinical Trials Utilizing Intermediate Endpoints and their Modulation by Chemopreventive Agents
NHLBI NIA	10/87	PA	Atherogenesis and Aging
NHLBI	10/87	RFA	Centers for the Study of Cardiovascular Disease in American Indians
NIDR	10/87	RFA	Research Centers on Oral Health in Aging
NICHD	10/87	RFA	Growth Factors and Hormones in Fetal and Infant Growth
NIDR	11/87	RFA	Specialized Caries Research Centers
NIDDK	11/87	PA	Prevention of Gallstones

NIDDK	12/87	RFA	Endocrine Aspects of AIDS
NIDDK	12/87	RFA	Endocrine Basis of Wasting in AIDS
NHLBI	12/87	PA	Hypertension, Diabetes and the NIDD Vasculature
NIDDK NHLBI	12/87	RFA	Cystic Fibrosis Research Centers
NICHD NIDDK	1/88	RFA	Biochemical Bases of Nutrient Function
NCI	1/88	RFA	Cancer Prevention Research Unit Program
NCI	1/88	RFP	Analysis of Fiber Components in Food
NIDDK	1/88	RFA	Digestive Diseases Core Centers
NHLBI	1/88	RFA	Evaluation of Physician Attitudes and Practice Regarding Cholesterol and Coronary Heart Disease
NCI	1/88	RFA	The Relationship Between Blood & Tissue Micronutrient Levels in Humans
NHLBI	2/88	RFP	Clinical Coordinating Center for a Registry of Patients with Severe Congenital Deficiency of Alpha-1-Antitrypsin
NCI	2/88	RFP	Literature Surveillance and Selection of Promising Natural Products
NIDR	2/88	RFP	International Collaborative Study of Oral Health Outcomes: U.S.A. Replication
NIDDK	3/88	RFA	Kidney Disease of Diabetes Mellitus: New Basic Studies of the Pathogenetic Mechanisms and Clinical and Epidemiologic Features
NIA NIDDK	3/88	PA	Role of Glycation in Aging and Diabetes
NCI	3/88	RFP	Dietary Surveys and Food Composition Data
NCI	3/88	RFA	Developmental Research in Special Populations
NICHD	3/88	RFA	Mental Retardation Research Centers
NIA NICHD	4/88	PA	Molecular Genetics of the Mammalian Sex Chromosomes and Aging
NIAMS	4/88	RFA	Association of Arthritis and Musculoskeletal Diseases with HIV Positivity and AIDS
NHLBI	4/88	RFA	Iron Overload: Cooley's Anemia and Other Disorders
NIDDK	5/88	RFA	Diabetes Centers
NIAID	5/88	RFA	Asthma and Allergic Disease Centers

NIA	5/88	PA	Gender and Aging: Relation to Health and Longevity
NIAID	5/88	RFA	Centers for Interdisciplinary Research on Immunologic Diseases
NCI	6/88	RFA	Data-based Intervention Research for Public Health Agencies
NHLBI	7/88	RFA	Hyperglycemia and Cardiovascular Disease Risk Factors: Field Centers, Coordinating Center and Support Laboratories
NCI	7/88	RFA	Prevention Clinical Trials Utilizing Intermediate Endpoints and their Modulation by Chemopreventive Agents
NCI	8/88	PA	Small Grants Program for Epidemiology
NIA	8/88	PA	Cross-National Investigations of the Epidemiology of Alzheimer's Disease and Other Dementias of Later Life
NIEHS	9/88	PA	Effect of Environmental Agents on the Endocrine System
NIA	9/88	RFA	Immunogerontology Program
NIDDK	9/88	RFA	Cystic Fibrosis Research Centers
NIA NIAMS	9/88	PA	Type II Osteoporosis

NIH Guide Notices

ODP/NCC	2/88	Notice	Availability of Fish Oil Test Material

NIH AWARD MECHANISMS

The NIH relies on three major instruments for accomplishing its program goals through the efforts of scientists outside the NIH. The mechanisms are financial assistance awards (grants and cooperative agreements) and acquisition awards (contracts).

Financial Assistance Awards

Grants. Grants for health-related research projects or activities make up the largest category of funding provided by the NIH. These grants encourage and support meritorious projects or programs in all scientific fields related to health, and span the spectrum from basic and applied research in laboratory and clinical settings to the evaluation, demonstration, and dissemination of new medical technologies. In addition, grants are awarded to create and sustain certain special resources or facilities for such research.

Grants are awarded to nonprofit organizations and institutions, governments and their agencies, and to individuals and for profit organizations for the support of research in health, medicine, and allied fields. Grants provide funds for salaries, equipment, supplies, travel, and other allowable direct costs of the research as well as for indirect costs. Through the grant mechanism, the NIH supports research projects, centers, career development and other research programs.

Grants are used when the idea for the research or training project is initiated by the investigator; when no substantial program involvement is anticipated between the funding BID and the recipient during performance of the activity; and there is no expectation on the part of the funding BID for delivery of a specified product or service. A grant may provide funds for essentially all reasonable costs of the activity. Grant applications may request, in most instances, an approximate amount of financial support and the duration of time, usually no more than 5 years, needed to complete the project. Funding is accomplished in annual increments.

Most applications for grant support originate with an individual investigator who develops a proposed plan for research or research training within an area of interest to NIH. In addition, NIH employs a variety of mechanisms to stimulate submission of applications in areas of high priority or special concern, including program announcements (PAs) and requests for applications (RFAs).

Cooperative Agreements. Cooperative agreements are similar to grants in that they are awarded by NIH to assist and support research and related activities. They differ, however, in that grants require minimal involvement of the awarding BID during the performance of project activities, but cooperative agreements give a substantial programmatic, i.e., scientific/technical, role to the BID. This role may involve cooperation or coordination to assist awardees in carrying out the project or review and approval of certain processes/phases in the scientific management of the project.

Policies and procedures for application, review, and administration of cooperative agreements are similar to those for grants. An important difference, however, is that the unit issues a specific program announcement or RFA describing the program, functions(s), or activities that it proposes to support by cooperative agreement and the nature of the proposed staff involvement. Terms and conditions, above and beyond those required for the normal stewardship of grants, must be negotiated in order to establish the rights, responsibilities, and duties of the prospective awardee and the NIH awarding unit, based on the terms and conditions outlined in the program announcement or RFA.

Eligibility. Assistance awards may be made to public and private organizations and institutions that sponsor and conduct biomedical research and development. These include universities, medical and other health professional schools, colleges, hospitals, research institutes, commercial organizations and Federal institutions. Foreign institutions and international organizations are also eligible to receive selected research awards. Detailed information regarding allowable costs can be found in the Public Health Service Grants Policy Statement. Readers are encouraged to consult their institutional business officers on such administrative matters.

There is no specific restriction on the number or dollar amount of most awards that may be made to any one institution or on behalf of any one investigator. However, in the latter case, the ability of a scientist to devote adequate time to the project, whether or not any part of his or her salary comes from the award, is a factor in the review of the application.

Application Forms. Applicants must provide detailed information to justify their proposals. Instructions are included in the research grant application kit (Form PHS 398), which may be obtained from the Division of Research Grants, National Institutes of Health, Bethesda, MD 20892, (301) 496-7441.

Application Receipt Dates. Unless otherwise specified in the announcement of a competitive opportunity, applications to the NIH are to be received by DRG in accordance with the following schedule:

- January 10, May 10, and September 10 for individual and institutional National Research Service Award (training grant and fellowship) applications;
- Feb 1, June 1, and October 1 for new research grant and Research Career Development Award applications as well as all program project and center applications;
- March 1, July 1, and November 1 for competing continuation and supplemental research project grant applications and amendments for traditional research project grants, FIRST Awards, and Research Career Development Awards; and
- April 15, August 15, and December 15 for Small Business Innovation Research grant applications.
- January 2, May 1, and September 1 for unsolicited AIDS grant applications submitted for expedited review including revised applications.

Assignment and Referral. In DRG, an application is first examined for relevance to the NIH, after which it is assigned both to an initial review group (IRG) for scientific merit review and also to an awarding unit for a second level review and consideration for possible funding. Applicants are notified by mail of these assignments.

Review Process. Applications are subjected to a peer review process that is based upon two sequential levels of review, both of which are required by law. The first level of review is performed by initial review groups (often called study sections) composed of at least 75 percent non-Federal scientists selected for their competence in particular scientific areas. An NIH health scientist administrator serves as executive secretary of the review group. The task of the IRGs is to evaluate the grant application for scientific and technical merit.

In considering the scientific merit of each application, the members of the IRG assess:

- scientific, technical, or medical significance and originality of the proposed research;
- appropriateness and adequacy of the experimental approach and methods to be used;
- qualifications and experience of the principal investigator and staff in the area of proposed research;
- reasonable availability of resources necessary to the proposed research;
- reasonableness of the proposed budget and duration in relation to the proposed research; and
- where an application involves activities that could have an adverse effect upon humans, animals, or the environment, the adequacy of the proposed means for protecting against such effects.

For each application, a recommendation of approval, disapproval, or deferral for additional information is made by majority vote. In addition, for each application recommended for approval, each member of the IRG individually and privately records a numerical score that reflects a personal evaluation of the relative scientific merit of the proposed research or training. The executive secretary uses these scores to calculate a priority score for each project. Priority scores assist the staff of the BID in determining which applications are to be funded.

After the IRG meets, the executive secretary prepares a summary statement for each application and forwards it to the appropriate BID for review by its council or board. A copy of the summary statement is also automatically sent to the principal investigator by the BID. The summary statement contains a description and critique of the proposed activity, an explanation of the recommendation of the IRG, a recommended budget, and notations about any special points such as a split vote or a potentially hazardous experimental procedure.

The second level of review of applications is made by the national advisory council or board associated with the awarding BID. These groups are composed of both scientific and lay representatives who are chosen for their expertise, interest, or activity in matters related to the individual BID missions. Council or board recommendations are based on judgments about scientific merit and relevance to BID program goals. In general, the NIH may make an award only if the application has been recommended for approval by both an IRG and a national advisory council or board.

Research Grants

Research Project Grants. Research project grants are awarded to an institution on behalf of a principal investigator to facilitate pursuit of a single scientific focus or objective in the area of the investigator's interest and competence. Institutional sponsorship assures the NIH that the institution will provide facilities necessary to accomplish the research and will be accountable for the grant funds. A research grant may rarely be awarded directly to an individual who has access to adequate facilities and resources for conducting the research. Applications are accepted for health-related research and development in all areas within the scope of NIH's mission.

FIRST Award. The First Independent Research Support and Transition (FIRST) Award, which supports a research project, is designed to encourage newly independent biomedical investigators in basic or clinical science disciplines. The FIRST Award, generally for 5 years, helps a research scientist who has completed training bridge the transition to independent investigator status.

Program Project Grants. Program project grants are awarded to institutions on behalf of a principal investigator for the support of a broadly based, often multidisciplinary, long-term research program with a particular major objective or theme. A program project involves the organized efforts of groups of investigators who conduct research projects related to the overall program objective. The grant can provide support for the projects and for certain shared resources needed for the total research effort. Each project supported under a program project grant is expected to contribute to the overall program objective.

Center Grants. Center grants, awarded to institutions on behalf of a program director and a group of collaborating investigators, provide support for long-term multidisciplinary programs of research and development. The distinction between program project and center grants is that center grants are more likely to have a clinical orientation and are usually developed in response to announcements of the specific needs and requirements of a BID. Center grants support programs in critical health problem areas including: research and development; demonstration of advanced techniques for the diagnosis, treatment, prevention, or control of disease; education; and other related nonresearch components.

Although center grants may support both the projects and the "core" of shared resources, in some instances only "core" costs are provided under the center grant, and project support must be requested through the project or program project grant mechanism. The staff of the appropriate BID should be consulted before a center grant application is submitted for review.

AREA Award. The Academic Research Enhancement Award (AREA) is designed to enhance the research environment of educational institutions that have not been traditional recipients of NIH research funds. This award provides limited funds for faculty members of these institutions to develop new research projects or expand ongoing research activities in areas related to the health sciences.

Resource Grants. Resource grants support research resources such as computer centers or general clinical research centers operating on an institutional, regional, or national basis. While the resources supported normally serve a wide range of biomedical research, they may be oriented toward specific research needs.

Conference Grants. The NIH provides funding for conferences planned for the purpose of coordinating, exchanging, and disseminating information related to its program interests. Generally, such awards are limited to participation with other organizations in the support of conferences rather than provision of sole support. Among the costs eligible for support are salaries, consultant services, equipment rental, travel, supplies, conference services, and publications. Prospective applicants are encouraged to inquire in advance concerning possible interest on the part of an awarding BID and to obtain more information on application procedures and costs eligible for support.

Workforce Development

Workforce development in nutrition research is enhanced through such mechanisms as the Research Scientist Development Awards, Modified Research Career Development Awards, Academic/Teacher Awards, Clinical Investigator Awards, Physician Scientist Awards, Physician Scientist Awards for Dentists, and the Dentist Scientist Award. Some of these are briefly described below.

- Research Scientist Development Awards support scientists who are committed to research and need advanced research training and additional experience.
- Modified Research Career Development Awards foster the development of young scientists with outstanding research potential for careers of independent research in the sciences related to health.
- Academic/Teacher Awards create and encourage a stimulating approach to disease-specific curricula that will attract high-quality students, foster academic career development of promising young teacher-investigators, develop and implement excellent multidisciplinary curricula through an interchange of ideas, and enable the grantee institution to strengthen its existing teaching program. The academic and teacher investigator awards are not used by all of the institutes.
- Clinical Investigator Awards provide the opportunity for promising medical scientists (with demonstrated aptitude to develop into independent investigators) or faculty members to pursue research aspects of categorical areas applicable to the awarding unit, and aid in filling the important academic faculty gap in these shortage areas within health professional institutions of the country.
- Physician Scientist Awards (Individual) support a newly trained clinician nominated by an institution for the development of independent research skills and experience in a fundamental science.
- Physician Scientist Awards for Dentists (Individual) support a clinically trained dentist nominated by an institution for the development of independent research.
- Dentist Scientist Awards (individual and institutional) support newly trained dentists to enhance their clinical training and obtain basic science research training.

Training Grants and Fellowships

The NIH supports the training of scientists for careers in the behavioral and biomedical sciences. Training opportunities are provided primarily through National Research Service Awards (NRSAs) and Fogarty International Fellowships.

National Research Service Awards. The major objectives of these awards are 1) to increase the number of individuals trained for research and teaching in specifically designed biomedical areas, and 2) to improve the environment in which the biomedical training is conducted. NRSA awards are made to U.S. citizens, noncitizen nationals, or individuals that have been lawfully admitted to the U.S. for permanent residence. Several of the most common types of NRSA awards are described below:

- *Postdoctoral individual NRSAs*, commonly known as "fellowships," are awarded to provide postdoctoral research training to qualified individuals who have received a Ph.D., M.D., D.D.S., or equivalent degree. The award provides the opportunity to carry out supervised research to enable biomedical scientists, clinicians, and others to broaden their scientific backgrounds and expand their potential for research in health-related areas. Each applicant must arrange to work with a particular sponsor affiliated with an institution that has the staff and facilities needed for the proposed training. The institutional setting may be a domestic or foreign nonprofit, private, or public institution, including NIH and ADAMHA.
- *Institutional NRSAs*, commonly known as "training grants," are awarded to domestic nonprofit, private, and non-Federal public institutions to support a training program in biomedical research at the predoctoral and postdoctoral levels. The applicant institution must have or be able to develop the staff and facilities required for the proposed program, and is responsible for the selection and appointment of trainees. Institutional grants may be made for periods up to 5 years and may be renewed. However, an individual may not receive more than 8 years of support in the aggregate from an NRSA (5 years predoctoral support and 3 years postdoctoral support) unless a waiver is granted by the responsible Public Health Service agency.
- *Senior fellowships* are designed to provide opportunities for experienced scientists to make major changes in the direction of their research careers, to acquire new research capabilities, to broaden their scientific background, to enlarge their command of an allied research field, or to take time from regular professional responsibilities to increase their capabilities for engaging in health-related research. Investigators who hold a doctorate or equivalent degree and have had at least seven subsequent years of relevant research or professional experience may apply for senior fellowships. The award is granted for 1 year, with continued support not to exceed 24 months contingent upon the research training plan, satisfactory progress and the availability of funds.

Fogarty International Fellowships. To further international cooperation and health research, the Fogarty International Center provides for and administers International Postdoctoral Fellowship programs for foreign scientists to study in the U.S. and for U.S. scientists to study abroad.

Acquisition Awards

Contracts. NIH awards research and development (R&D) contracts to academic institutions and other nonprofit and commercial organizations for specific scientific inquiry directed towards particular areas of research and development needed by the NIH or U.S. Government. In these circumstances the NIH wishes to utilize advances in knowledge and technology to search for solutions to specific questions. Contract performance is monitored closely by NIH to ensure accomplishment of contract goals for the benefit of or use by the awarding BID, the NIH, or the Government.

Most NIH R&D contracts are of the cost-reimbursement type, where the NIH pays contractors allowable, allocable, and reasonable costs in performing the project. In addition to reimbursable costs, a fee may be paid where appropriate.

The review process for solicited R&D contracts differs from that for grants in that all offerors respond to a Government-defined statement of work contained in a solicitation document called a request for proposal. Proposals responding to the solicitation are evaluated against fixed evaluation criteria specified in the RFP. Consistent with statutory and regulatory requirements for peer review of NIH solicited contract projects, the concepts of each requirement and the contract proposals are evaluated by scientific peer review groups composed of at least 75 percent non-Federal advisors who provide recommendations regarding the merits of the basic purpose, scope, and objectives of proposed projects, and the relative merits of each proposal.

In order to reach all segments of the scientific community, contract opportunities and requirements are advertised as widely as possible. Solicitation announcements appear in the *Commerce Business Daily*. (Subscriptions are available from the Superintendent of Documents, Government Printing Office, Washington, D.C. 20402.) Announcements of RFP availability are also published in the *NIH*

Guide for Grants and Contracts. Some project solicitations may also appear in scientific and medical journals or other pertinent publications.

R&D contract proposals responding to NIH solicitations undergo review by advisory peer evaluation groups whenever RFPs seek offerors for innovative and original approaches to accomplish tasks described in our solicitations. All proposals are evaluated strictly in accordance with evaluation criteria specified in the RFP. All of the tasks should be accomplished. All proposals are evaluated strictly in accordance with the evaluation criteria indicated in the RFP.

Recommendations of peer reviewers, and the results of separate NIH staff evaluations of technical and cost proposals, provide the basis for negotiations with offerors in a competitive range. At the conclusion of these discussions, offerors are requested to submit a best and final offer, which then serves as the basis for selection of offerors for award(s).

BIDs occasionally make awards in response to unsolicited contract proposals when they meet specific NIH program needs and when adequate justification exists for a noncompetitive award. In these instances, peer reviews may simultaneously evaluate both the concept and the approach for the proposed project. Subsequent evaluations and negotiations are similar to those for solicited proposals.

Research Contracts. These contracts are for specific research problems identified by NIH components and require BID developed contractor performance requirements and Government monitoring to ensure that the contract objectives are met. They include projects to: evaluate chemotherapeutic modalities against cancer; explore the safety and efficacy of regimens to control heart attacks; characterize immunological phenomena to extend organ transplant capabilities, etc.

Other Contracts. Other contract mechanisms used at NIH include Development Contracts, Demonstration Contracts, Small Business Set-Asides, and 8(a) Set-Asides (socially or economically disadvantaged firms). Details on these and other contract mechanisms may be obtained from the publications cited at the end of this appendix under "Information Sources at NIH."

Clinical Trials

Clinical trials in nutrition are supported by each of the major mechanisms discussed above--research grants, contracts, and cooperative agreements. A clinical trial is defined as a scientific research activity undertaken to define, prospectively, the effect and value of prophylactic/diagnostic/therapeutic agents, devices, regimens, procedures, etc., applied to human subjects. The study must be prospective, and intervention of some sort must occur. The number of cases or patients depends on the hypothesis being tested, but must be sufficient to permit anticipation of a definite, statistically significant result. Phase 1, feasibility, or pilot studies are excluded by definition.

Information Sources at NIH

The *NIH Guide for Grants and Contracts*, published approximately weekly, describes programs at the NIH, announces new programs, Requests for Applications, and Requests for Proposals, and provides policy guidance. Copies of the Guide may be found in many research and medical libraries. In addition, principal investigators, business officers, and others not presently receiving the Guide may be included on the mailing list by requesting a form from the Office of Extramural Research. To obtain this form, or for general information on NIH extramural programs, please contact:

Institutional Liaison Office
Office of Extramural Research
National Institutes of Health
Bethesda, Maryland 20892
(301) 496-5366

The Office of Grants Inquiries in the Division of Research Grants serves as a focal point for information on NIH grant programs and application procedures. Relevant publications and single copies of application kits (if not available at an organization's application control office) may be obtained from:

Office of Grants Inquiries
Division of Research Grants
National Institutes of Health
Bethesda, Maryland 20892
(301) 496-7441

Questions regarding the extramural programs of a particular BID or a specific grant or contract should be directed to the awarding unit concerned. Addresses and telephone numbers are provided for each BID in Section 2 of this publication.

Publications

Further information concerning the NIH extramural programs is available from the following publications:

- *NIH Extramural Programs: Funding for Research and Research Training.* U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Office of Extramural Research and Training. NIH Publication No. 88-33, May 1988.
- *NIH Grants and Awards.* U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Division of Research Grants, Office of Grants Inquiries. September 1987.

APPENDIX D

NCC-SPONSORED CONFERENCES AND WORKSHOPS, FY 1988

NIDDK	Seminar on Omega-3 Fatty Acid Deficiency in Sub-Human Primates, and Its Implications for Humans, December 2, 1987
NCI	Second International Factored Food Vocabulary Workshop, January 20-22, 1988
NICHD	Workshop on Nutritional Therapy of Inborn Errors of Metabolism, March 8, 1988
NICHD, NIDDK	Childhood and Its Role in Adult Obesity, April 5, 1988
NCI	Workshop on Folic Acid, Methylation and Cancer Prevention, April 21-22, 1988
NICHD	Workshop on Nutritional Aspects of Human Milk, May 6, 1988
NICHD	Nutrition and Fitness, May 21-26, 1988
NIA	Nutrition and Aging at FASEB, May 2-5, 1988
NIA	The Role of Folate and Vitamin B_{12} in Neurotransmitter Metabolism and Degenerative Neurological Changes Associated with Aging, May 19-20, 1988
NIDDK	Health Effects of Westernization of the Diet, June 7, 1988 (Working meeting of U.S. Panel of U.S.-Japan Malnutrition Panel)
NIA	Maillard Reaction in Aging, Diabetes, and Nutrition, September 22-23, 1988
NIAID	Occupational Diseases Due to Exposure to Food Allergens, September 8-9, 1988
NCI	Working Group Meeting Clinical Opportunities for Diet Modification: A Guide for the Busy Clinician, September 8-9, 1988
NIA	The Potential for Nutritional Alteration of the Aging Process, September 13-15, 1988
NIA	The International Conference on Longevity and Aging, September 13-15, 1988

APPENDIX E

NUTRITION EDUCATION SUBCOMMITTEE PROCEDURES

All nutrition publications and materials prepared for the public by any of the 12 institutes or 2 divisions of the National Institutes of Health are to be brought to the attention of the NIH Nutrition Education Subcommittee for review and comment. Adherence by the institutes to the subcommittee's recommendations is required and all revisions of publications/materials are to be brought to the attention of the Education Subcommittee chairperson before their final publication.

PROCESS

The BID information officers and/or NCC members are to bring to the attention of the Education Subcommittee chairperson all nutrition publications/materials destined for the public when they are close to the final draft stages, prior to their review for institute clearance review.

- The Education Subcommittee is asked to review and comment on the draft and provide comments to the chairperson within 2 weeks. The comments are then collated and discussed at a meeting of the subcommittee in the presence of the appropriate initiating institute staff. The final comments evolving from the subcommittee meeting are then transmitted to institute staff and NCC members for action.
- Problems with incorporating the subcommittee's comments are to be discussed and resolved with the subcommittee chairperson and respective BID-NCC representative. If such problems are not resolved, the entire NCC will be asked to provide comment. The revised version of the publication is to be brought to the attention of the chairperson to assure accuracy and consistency. Depending on the extent of the revision, a second review by the entire subcommittee may be required.
- After the publication has been cleared by the institute, the final revised version is to be brought to the attention of the Education Subcommittee chairperson.
- Sample copies of all printed publications and information regarding availability should be provided to the Education Subcommittee chairperson and the NCC office in order to keep up-to-date the list of nutrition publications available to the public from the various NIH institutes.

CONTENT

Each publication is reviewed for the following:

- Scientific accuracy. All information is based on the best current scientific evidence. Areas known to be controversial also need to be addressed to avoid misinterpretation by the public.
- Consistency with other NIH nutrition publications to avoid mixed messages.
- Compatibility with the "Dietary Guidelines for Americans." Since the guidelines serve as the basis for all Federal dietary guidance to the general public, publications directed toward most healthy Americans must support the tenets of the dietary guidelines.
- Identification of the intended audience (e.g., adults, children, and etc.) and the ability to meet the specific needs of the intended target group, be it the healthy general public or other subpopulation groups (e.g., patient populations, minority groups, and etc.). For example, the reading level needs to conform to the needs of the target audience, and publications should be culturally relevant.
- Avoidance of mention of specific brand names of foods or other items that can be misconstrued as NIH endorsement.
- Appeal and clarity of the overall publication, title, graphs, illustrations, and charts to illustrate difficult concepts.

NIH NUTRITION PUBLICATIONS REVIEWED BY THE NIH NUTRITION EDUCATION SUBCOMMITTEE AND AVAILABLE TO THE PUBLIC

Publications are available by NIH publication number from the offices listed. The address for all offices is National Institutes of Health, Bethesda, MD 20892.

National Cancer Institute
Office of Cancer Communications (Building 31, Room 10A18):
- *Good News, Better News, Best News...Cancer Prevention* (84-2671)
- *What Black Americans Should Know About Cancer* (82-1635)
- *Diet, Nutrition, and Cancer Prevention... A Guide to Food Choices* (for health professionals; 87-2711)
- *Diet, Nutrition, and Cancer Prevention... The Good News* (87-2878)

National Heart, Lung, and Blood Institute
Information Office (Building 31, Room 4A21):
- *Questions About Weight, Salt, and High Blood Pressure* (84-1459)
- *NHLBI Facts About Blood Cholesterol* (revision; 88-2696)
- *Healthy Heart Handbook for Women* (87-2720)

National Institute on Aging
Information Office (Building 31, Room 5C35):
- *Be Sensible About Salt* (Age Page)
- *Osteoporosis: The Bone Thinner* (Age Page)
- *Dietary Supplements: More Is Not Always Better* (Age Page)
- *Nutrition: A Lifelong Concern* (Age Page)
- *Hints for Shopping, Cooking, and Enjoying Meals* (Age Page)

National Institute of Dental Research
Information Office (Building 31, Room 2C34):
- *A Healthy Mouth for You and Your Baby* (86-1255)
- *Fluoride to Protect Your Children's Teeth* (Fact Sheet)
- *Fluoride to Protect the Teeth of Adults* (87-2329)
- *Prevent Baby Bottle Tooth Decay* (Fact Sheet)

National Institute of Diabetes and Digestive and Kidney Diseases
Information Office (Building 31, Room 9A04):
- *Irritable Bowel Syndrome* (85-693)
- *Noninsulin Dependent Diabetes* (87-241)

National Institute of Arthritis and Musculoskeletal and Skin Diseases
Information Office (Building 31, Room 9A04):
- *Osteoporosis - Cause, Treatment, and Prevention* (86-2226)
  (To obtain a single copy of this publication, send a business-size, self-addressed envelope with $0.50 postage to the address listed. Currently, quantities and postage and handling charges are as follows: 10 copies for $2; 25 copies for $5; or 50 copies for $10. All orders must be prepaid. Checks or money orders must be made to AMS Clearinghouse.)

Division of Nutrition Research Coordination
(Building 31, Room 4B63):
- *Nutrition Research at the NIH* (89-2611)

APPENDIX F

HNRIM CLASSIFICATION SYSTEM CODES

The development of the Human Nutrition Research and Information Management (HNRIM) System began with the work of the NCC. Since 1977, the NCC has retrieved data on NIH projects with nutrition research and training components and their nutrition expenditures, based on the definition of human nutrition research developed by the NCC.

The Joint Subcommittee on Human Nutrition Research, operating out of the Office of Science and Technology Policy in the Executive Office of the President, expanded the NIH definition and data collection system to include the human nutrition research activities supported by participating Federal agencies, and developed a system of 34 data classification categories for human nutrition research.

The FY 1988 NIH nutrition research program is presented in accordance with this classification system, which is used by the HNRIM system. In FY 1985, Code 35, "Parenteral, Enteral, and Elemental Nutrition," was added under section I, subsection B, and the NIH Special Interest Areas were assigned codes 51-56.

I. Research in the Biomedical and Behavioral Sciences

A. Research on Normal Nutritional Requirements Throughout the Life Cycle

The following five categories are included because of the importance to health promotion of establishing normal nutritional requirements throughout the life cycle, and the differing needs of individuals at various stages of the life cycle.

Research activities relevant to normal nutrition at specific stages of the human life cycle should be assigned to classifications 1-5.

1. Maternal Nutrition

2. Infant and Child Nutrition (0-12 years)
(Includes the low birth weight infant)

3. Adolescent Nutrition (13-18 years)

4. Adult Nutrition (19-65 years)

5. Nutrition of the Elderly (65+ years)

B. Diseases and Conditions

Research on the role of nutrition in the prevention, amelioration, and treatment of diseases and conditions should be assigned to categories 6-16.

Because of the importance of appropriate nutritional support of the patient in the treatment of disease, the category of "parenteral, enteral, and elemental nutrition" has been added in this subsection as code 35.

6. Cardiovascular Disease and Nutrition

7. Cancer and Nutrition

8. Other Diseases and Nutrition
(E.g., osteoporosis, diabetes, etc.)

9. Trauma (Including Burns) and Nutrition

10. Infection--Immunology and Nutrition

11. Obesity, Anorexia, and Appetite Control

12. Genetics and Nutrition

13. Nutrition and Function
(Includes mental, psychomotor, and work performance; environmental stress)

* **14. Nutrient Interactions**
(Includes nutrient-nutrient interactions, nutrient-drug interactions, nutrient-toxicant interactions, and nutrient toxicity)

15. Other Conditions and Nutrition

* **16. Nutritional Status**
(Includes research on methods for the determination of nutritional status and surveillance: dietary history and food consumption, biochemical determinants, anthropometry, and clinical examination)

35. Parenteral, Enteral, and Elemental Nutrition

C. Nutrient Metabolism and Metabolic Mechanisms at the Cellular and Subcellular Levels

Categories 17-25, 14, and 27 classify research by nutrient variables; these categories should be used to indicate the nutrient variables in research classified elsewhere; and classify biochemical, subcellular, cellular, and animal research such as studies of nutrient mechanisms and metabolism not related to specific diseases, conditions, or stages of the life cycle.

17. Carbohydrates

18. Lipids (Fats and Oils)
(Includes essential fatty acids, lipo- and apoproteins)

19. Alcohols
(Includes ethanol, sorbitols, and other alcohols used as components in synthetic and semisynthetic foods)

20. Proteins and Amino Acids
(Includes essential as well as nonessential amino acids such as taurine and carnitine)

21. Vitamins
(Includes vitamins A, C, B_6, B_{12}, D, E, K, thiamin, riboflavin, niacin, folacin, biotin, and pantothenic acid)

22. Minerals and Essential Trace Elements
(Includes calcium, phosphorus, magnesium, iron, zinc, iodine, copper, manganese, fluoride, chromium, selenium, and molybdenum)

23. Water and Electrolytes
(Includes sodium, potassium, and chloride)

24. Fiber

25. Other Nutrients in Food
(Such as cobalt, nickel, vanadium, silicon, tin, arsenic, cadmium, choline, lecithin, and various growth factors)

***14. Nutrient Interactions**
(Includes nutrient-nutrient interactions, nutrient-drug interactions, nutrient-toxicant interactions, and nutrient toxicity)

***27. Bioavailability of Nutrients**
(Includes methods for the determination of bioavailability of nutrients)

II. Research in Food Sciences

Categories 26-29 should be used for research in the nutritional aspects of food sciences.

26. Food Composition
(Includes nutritional quality, nutrient content, and research on methods of analysis for nutrients and fiber)

***27. Bioavailability of Nutrients**
(Includes methods for the determination of bioavailability of nutrients)

28. Effects of Technology on Acceptability and Nutritional Characteristics of Foods and Diets
Includes the beneficial and adverse effects of varietal and species differences, harvest and post-harvest technology, retail food practices, food processing, handling, preservation, and home cooking)

29. Other Research in Food Sciences

III. Research on Nutrition Monitoring and Surveillance of Populations

30. Food Consumption Surveys
(Includes research on methods for determination of food consumption and its trends, and research utilizing data derived from such surveys)

31. Studies of Dietary Practices, Food Consumption Patterns, and Their Determinants

***16. Nutritional Status**
(Includes research on methods for the determination of nutritional status and surveillance: dietary history and food consumption, biochemical determinants, anthropometry, and clinical examination)

IV. Research in Nutrition Education

Categories 32-33 encompass research in nutrition education.

32. Studies on Methods for Informing and Educating the Public About Nutrition, Health, and Dietary Practices and for Countering Nutrition Misinformation
(Includes studies on methods for informing and educating professionals in these areas.)

33. Other Research in Nutrition Education

V. Research on the Effects of Government Policy and Socioeconomic Factors on Food Consumption and Human Nutrition

34. Effects of Government Policy and Socioeconomic Factors on Food Consumption and Human Nutrition

VI. NIH Special Interest Areas

Codes 51-56 have been assigned to special interest areas of the NIH and are used only by the NIH.

51. Prevention of Disease

52. International Research

53. Epidemiological Research

54. Education for Professionals

55. Education for the Public

56. Clinical Trials

*Codes marked by an asterisk are applicable to more than one class.

ABBREVIATIONS

ACRF	Ambulatory Care Research Facility
ADA	adenosine deaminase
ADAMHA	Alcohol, Drug Abuse, and Mental Health Administration
AGE	advanced glycosylation end
AID	Agency for International Development
AIDS	acquired immunodeficiency syndrome
ALS	amyotrophic lateral sclerosis
AMD	age-related macular degeneration
AREA	Academic Research Enhancement Award
ARS	Agricultural Research Service
ATP	adult treatment panel
BCG	Bacillus Calmette-Guérin
BHT	butylated hydroxytoluene
BIDs	bureaus, institutes, divisions
BLSA	Baltimore Longitudinal Study of Aging
BMI	body mass index
BMR	basal metabolic rate
BPD	bronchopulmonary dysplasia
CATCH	Child and Adolescent Trial for Cardiovascular Health
CC	Clinical Center
CHD	coronary heart disease
CNRUs	Clinical Nutrition Research Units
CNS	central nervous system
CPRP	Cancer Prevention Research Program
CVD	cardiovascular disease
DBP	diastolic blood pressure
DCCT	Diabetes Control and Complications Trial
DDE	metabolite of DDT
DDT	dichlorodiphenyltrichloroethane
DHA	docosahexaenoic acid
DHHS	Department of Health and Human Services
DISC	dietary intervention in school children (study)
DLA	Division of Legislative Analysis
DNA	deoxyribonucleic acid
DNCP	Diet, Nutrition, and Cancer Program
DNRC	Division of Nutrition Research Coordination
DOC	Department of Commerce
DOD	Department of Defense
DRR	Division of Research Resources
DRS	Division of Research Services
EDI	Eating Disorder Inventory
EPA	eicosapentaenoic acid
ESF	European Science Foundation
FDA	Food and Drug Administration
FFF	foreign-funded fellowship
FIC	Fogarty International Center
FIRST	First Independent Research Support and Transition
FOTMAC	Fish Oil Test Materials Advisory Committee
FY	fiscal year
GCRC	General Clinical Research Centers
GRC	Gerontology Research Center
HDL	high density lipoprotein

HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HNIS	Human Nutrition Information Service
HNRCs	Human Nutrition Research Centers
HNRIM	Human Nutrition Research and Information Management
ICHNR	Interagency Committee on Human Nutrition Research
INCNM	Interagency Committee on Nutrition Monitoring
IRBP	Interphotoreceptor Retinoid-Binding Protein
IRG	Initial Review Group
IRF	international research fellowship
LBW	low birth weight
LDL	low density lipoprotein
LRC	Lipid Research Clinic
MEN-2A	multiple endocrine neoplasia
MOU	memorandum of understanding
MRFIT	Multiple Risk Factor Intervention Trial
NASA	National Aeronautics and Space Administration
NCC	Nutrition Coordinating Committee
NCEP	National Cholesterol Education Program
NCHS	National Center for Health Statistics
NCI	National Cancer Institute
NCNR	National Center for Nursing Research
NEI	National Eye Institute
NES	Nutrition Education Subcommittee
NFT	neurofibrillary tangle
NGHS	National Growth and Health Study
NHANES	National Health and Nutrition Examination Survey
NHBPEP	National High Blood Pressure Education Program
NHLBI	National Heart, Lung, and Blood Institute
NIA	National Institute on Aging
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD	National Institute of Child Health and Human Development
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIDR	National Institute of Dental Research
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
NNMS	National Nutrition Monitoring System
NOAA	National Oceanic and Atmospheric Administration
NPB	Nutrition Policy Board (DHHS)
NPY	neuropeptide Y
NSF	National Science Foundation
NSRA	National Research Service Awards
NTIS	National Technical Information Service
NTP	National Toxicity Program
OATase	ornithine aminotransferase
OD	Office of the Director
ODP	Office of Disease Prevention
ODPHP	Office of Disease Prevention and Health Promotion (DHHS)
OECD	Organization for Economic Cooperation and Development
OSTP	Office of Science and Technology Policy
P-P	pellagra-preventive
P/S	polyunsaturated/saturated fat
PABA	para-aminobenzoic acid

PAHO	Pan American Health Organization
PAs	program announcements
PCBs	polychlorinated biphenyls
PCM	protein-calorie malnutrition
PD	Parkinson's disease
PET	positron emission tomography
PEM	protein energy malnutrition
PERC	Perinatal Emphasis Research Center
PHS	Public Health Service
PKU	phenylketonuria
PSO	posterior subcapsular opacities
RCDAs	research career development awards
RCS	Royal College of Surgeons
RDAs	recommended dietary allowances
RFAs	requests for applications
RFLP	restriction-fragment-length polymorphism
RFPs	requests for proposals
RNA	ribonucleic acid
SIF	senior international fellowship
SIV	simian immunodeficiency virus
SPRA	Special Program for Research on Aging
TAIM	Trial of Antihypertensive Intervention Methods
TAP	T-cell activating protein
TOHP	Trials of Hypertension Prevention
TPN	total parenteral nutrition
USDA	U.S. Department of Agriculture
UWL	unstirred water layer
VA	Veterans Administration
VLBW	very low birth weight
VLDL	very low density lipoprotein
VRB	Veterinary Resources Branch
WHO	World Health Organization

DISCRIMINATION PROHIBITED

Under provisions of applicable public laws enacted by Congress since 1964, no person in the United States shall, on the ground of race, color, national origin, handicap, or age, be excluded from participation in, be denied the benefits of, or be subjected to discrimination under any program or activity (or, on the basis of sex, with respect to any education program or activity) receiving Federal assistance. In addition, Executive Order 11141 prohibits discrimination on the basis of age by contractors or subcontractors in the performance of Federal contracts, and Executive Order 11246 states that no federally funded contractor may discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin. Therefore, the Nutrition Coordinating Committee must be operated in compliance with these laws and Executive Orders.

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